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CHRONIC LEAD POISONING

A REVIEW OF SEVEN YEARS' EXPERIENCE AT THE CHILDREN'S HOSPITAL, DISTRICT OF COLUMBIA

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THE purpose of this article is to review seven years' experience with the problem of chronic lead poisoning in infants and children in a large children's hospital, and to consider this experience in the light of previous reports.

BACKGROUND

Lead poisoning is still a significant cause of mortality and morbidity in children. Although only 19 cases were reported by Millichap and associates[1] in Great Britain in the 50 years ending in 1952, most American reports indicate a much higher incidence.[2-8] Without question the most important cause of chronic lead intoxication in children is ingestion of lead-containing substances. Scattered small epidemics of acute intoxication due to inhalation of lead fumes from burning storage battery casings have been reported.[9] Of the substances ingested by children, the most widely reported are paint from walls and woodwork and plaster.[1-5, 7, 8] Other sources are painted furniture and painted or lead toys. In earlier times, lead nipple shields and body powders containing lead were common sources.

In most reported series, the age range of children with lead intoxication is from 1 to 4 years,[3, 5-7, 10] the time of life when incidence is highest for all acute toxic ingestions. However, since only small amounts of lead can be absorbed and retained at one time, the abnormal appetite, or pica, to cause toxicity, must persist for several months.

The psychological background of the pica associated with chronic lead intoxication has been studied by several authors[5, 7, 10] who have observed that most of these children lived in blighted or slum areas where flaking paint and loose plaster were abundant. In addition, personal supervision was limited because of the necessity for working parents to be away from home, the large number of children in the families, and the parents' ignorance of the dangers of lead ingestion. Although most of the children were apparently normal in intellectual and motor functioning prior to illness, they were often emotionally unstable and harder to handle than their siblings. The mother-child relationship was frequently abnormal as manifested by the

mother's indifferent or punishing attitude toward the child, her encouragement of the child's oral activity as a substitute for maternal attention, and/or occasionally significant emotional problems in the mother herself.

Most authors have noted a higher incidence of symptoms from lead poisoning in the summer months.[3, 4, 5, 7] Two possible reasons are: (1) the effect of increased solar radiation on the skin producing in the patient more vitamin D, which presumably aids in the absorption of lead, and (2) more frequent dehydration and acidosis which mobilize lead from depots.

There seems to be little correlation between the incidence of lead poisoning and sex or race of the patient.

A survey of geographical distribution of plumbism in children is currently being made by Dr. Howard M. Cann of the Clearing House for Poison Control Centers of the U. S. Public Health Service.

Symptoms, when present, almost always relate to the gastrointestinal or central nervous systems.[1-6, 8] Among the frequent and significant symptoms are anorexia, vomiting, constipation, abdominal pain, irritability, convulsions, drowsiness, incoordination, and pallor. Less commonly reported symptoms include personality change, tremors, and diarrhea. A prodrome of minor gastrointestinal symptoms, such as constipation or abdominal pain, and central nervous symptoms, such as lethargy, may precede by as much as two weeks the onset of more serious symptoms of vomiting, coma, or convulsions. Although the symptoms of lead intoxication are obviously nonspecific, their association with a history of pica may prove quite significant.

There are often no abnormal physical findings, especially when there is no severe central nervous system disease. Among the most commonly observed objective signs are pallor, motor weakness, coma, convulsions, papilledema, hyperreflexia, and ataxia.[1, 3-8] Respiratory center depression[11] and diaphragmatic paralysis[1] have also been reported. Lead lines on the gums, which are common in adult plumbism, are quite unusual in children.[12]

The pathologic changes due to lead intoxication are in general rather nonspecific.[3, 5, 13, 14] The brain may show edema, punctate hemorrhages, gliosis, and focal necrosis, while the liver and kidney may show characteristic acid-fast intranuclear inclusions as well as renal tubular cell abnormalities. A frequent finding is degeneration of anterior horn cells. When tissues have been analyzed for lead content,[3, 7] the bones have contained the highest concentration, the liver and kidneys next; the brain, even in the presence of severe clinical encephalopathy, contained the least amount.

In one of our cases of fatal lead encephalitis previously reported by Rice and associates,[13] no lead was extracted from the brain although high levels were found in bone, liver, and kidneys. These findings suggest either that lead is not a direct toxic agent to brain tissue, or that the brain is so sensitive that even minute amounts can cause significant damage.

Almost all children with chronic plumbism have a significant anemia with associated basophilic stippling of the red cells and elevated reticulocyte counts.[1, 3, 5, 6, 8] The stippling and anemia are possibly due to the interference by lead with the incorporation

of protoporphyrin into hemoglobin.[15] A recent report of lead intoxication in adults[16] notes that the erythroblasts in the marrow show consistent but not pathognomic changes. It has also been suggested[17] that the stipples might consist of protoporphyrin (possibly combined with lead). Coproporphyrin III is almost always found in increased concentration in the urine of patients with chronic lead intoxication,[3, 4, 17-20, 23] and there is a definite relationship of urinary concentration of porphyrins to the stippled red cell count but not to the degree of anemia.

Lines of increased density in the metaphyses of the long bones as seen by roentgenography are almost always present in children with plumbism.[3-5, 8] These lines are not diagnostic nor are they areas of increased lead deposition; actually they are areas of differential calcification.[21] Other bones may also show "lead lines"; Keefer and Mokrohisky[22] point out that careful study of routine chest roentgenograms may suggest the proper diagnosis.

The laboratory tests which confirm a diagnosis of chronic lead poisoning are the demonstration of abnormally high levels of lead in the blood and urine; i.e., above 50 to 60 μg per 100 ml. of blood, or above 80 μg per 1,000 ml. of urine, or per 24-hour specimen of urine. In children, whose 24-hour volume of urine excretion may be as small as 100 to 250 ml., it is more realistic to calculate lead excretion per liter of urine per 24 hours. The degree of elevation of these levels does not correlate with the severity of illness.[1, 3, 4, 15, 19, 21, 23]

Although there are many factors from history, physical examination, and laboratory study which are suggestive of lead intoxication, there is no single pathognomonic finding. Children may have no symptoms although their blood or urine lead concentrations are definitely above normal. Such children might receive a diagnosis of potential, subclinical, or asymptomatic lead poisoning. The most significant data for establishing a diagnosis are a definite history of pica for lead-containing substances, suggestive signs and symptoms, anemia with stippling, "lead lines" on x-ray, increased lead and coproporphyrin levels in the urine, and increased lead concentration in the blood. The final diagnosis rests on the clinician's judgment after evaluation of the data at hand.

Prior to the late 1940's, treatment of lead intoxication was directed at shifting lead from the blood and soft tissues to the bones, whence it could be excreted more slowly and under controlled conditions. Such therapy included diets high in calcium, phosphorus, and vitamin D followed by citric and other organic acids. Since 1950, dimercaprol (BAL) has been used with equivocal efficacy and potential toxicity.[1, 3, 4, 8, 12, 19, 21] In 1952, Bessman and associates[24] and Belknap[31] reported on the use of calcium disodium ethylenediamine tetraacetate (versenate, edathamil, or EDTA), a safe and effective chelating agent which binds lead into a nontoxic complex which is easily excreted in the urine.[3, 18-20, 23, 30] There has been mention of potential toxic effects of EDTA on bone marrow[21, 31] and renal function[24, 30] but these effects may have been coincidental and certainly have not been consistently reported. Although blood coagulation is prolonged in vitro by EDTA,[32] we have found

no reports of clinical bleeding dyscrasias resulting from use of this drug in therapy of plumbism. EDTA is quite effective when administered intravenously or subcutaneously, and probably when given intramuscularly, but no final agreement has been reached regarding the efficacy of its oral use. The dosage is now generally accepted to be 30 to 75 mg. per kilogram per 24 hours, but in the first published work it was 0.5 Gm. 3 times daily, regardless of weight. Most authors now suggest a plan in which the drug is given for 3 to 5 days, discontinued during a 2- or 3-day rest period, and then given for another 3 to 5 days. Since EDTA apparently combines with lead only in body fluids and soft tissues, the purpose of the rest period between courses of treatment is to allow the lead in the bone to re-establish equilibrium with the lead-depleted soft tissues. Rieders and associates[26] suggest intravenous therapy once weekly on an outpatient basis; however, cumulative excretion studies by Chisolm and Harrison[19] show that 4 or 5 days are required for deleading soft tissues. During EDTA therapy of lead intoxication, urine lead excretion may be increased from 10 to 100 times the pretreatment level.[18, 20, 23, 30] Hardy and associates,[20] working with adults, showed that in three normal patients the increase was only 6 to 11 fold compared with rises of 20 to 30 times in three patients with plumbism. Another good index of successful therapy is the drop in urinary coproporphyrin excretion.[18-20]

Reduction of cerebrospinal fluid pressure by mechanical methods has generally been a last resort in treating lead encephalopathy. Techniques used with varying success have been lumbar puncture[1, 19] and craniotomy.[3, 6, 18, 21, 22, 33] Results of more recent work suggest that when no improvement is evident during therapy with EDTA, extensive surgical decompression of the skull can be lifesaving and may even reduce potential residuals.[34]

The prognosis for life in chronic lead intoxication apparently depends more on severity and duration of illness than on type of therapy.[19] The usual mortality figures range from 10 to 25 per cent[2, 3, 5, 8, 25]; the fatal cases almost invariably were those with severe encephalopathy. The residual neurologic damage from lead intoxication is as distressing as the mortality. Significant sequelae have been reported in from 25 to 75 per cent of cases and include paralyses, blindness, and organic brain damage, especially in areas of visual-motor function and language skills.[2, 5, 8, 10] There is a much higher incidence of severe sequelae after severe encephalopathy,[19] but, in general, residuals are best correlated with continuing pica and, hence, continued active disease.[7]

DEFINITION AND CLASSIFICATION

During the period 1950 through 1956, 43 patients were treated at Children's Hospital, Washington, D. C., because of chronic lead poisoning. No cases of acute lead poisoning, such as is caused by inhalation of lead fumes, have been observed.

In the present study the diagnosis of lead poisoning was made on the basis of abnormal blood or urine lead levels prior to treatment and/or any two of the three following abnormalities: (1) pica of presumably lead-containing material, (2) punctate basophilic stippling of red blood cells on smear, or (3) markedly increased transverse densities in the metaphyses

of the long bones by roentgenography. Determinations of urine and blood lead levels were originally performed by hospital research facilities under the direction of Dr. S. P. Bessman, and more recently by the D. C. Department of Public Health Laboratory. No qualitative or quantitative urine coproporphyrin or stool lead studies were done.

An attempt has been made to group the patients into the following arbitrary classes: asymptomatic, lead intoxication without encephalitis, mild encephalitis, and severe encephalitis. The asymptomatic patients were children who had no apparent sign or symptom of lead intoxication but, during study of families of patients with plumbism or during study for other symptoms, were discovered to have a significant accumulation of lead within their bodies. The patients with simple lead intoxication had anemia and gastrointestinal complaints such as cramps or constipation. The severe encephalitic patients had prolonged convulsions or coma for as long as 24 to 48 hours, while the patients with mild encephalitis had central nervous symptoms and signs not including those of severe encephalitis.

TABLE I. TYPES OF CHRONIC LEAD POISONING IN 43 INFANTS AND CHILDREN, 1950-1956, AT CHILDREN'S HOSPITAL, DISTRICT OF COLUMBIA

TYPE	NO. OF PATIENTS		PER CENT	
Asymptomatic	12		28	
Clinical symptoms without encephalitis	14		32	
Encephalitis	17		40	
Mild	8		19	
Severe	9		21	
Total	43		100	

Table I shows that approximately 28 per cent of our 43 patients were asymptomatic and 40 per cent of the children had lead encephalitis. Obviously the proportion of encephalitis patients in any given series will color the mortality and morbidity of such a series and thus the effectiveness of therapy.

INCIDENCE AND ETIOLOGY

Distribution of cases according to age, sex, color, and season coincide, in general, with the patterns reported by other authors. The age group from 2 to 3 years contained 2½ times as many children as any other year, and the 1- to 3-year age group contained 75 per cent of the patients in this series.

Fig. 1.—Annual incidence of lead poisoning at the Children's Hospital of the District of Columbia.

There was no significant difference in the sex incidence in this series, but a ratio of approximately 3 Negroes to 1 white patient reflects the fact that our clinic and ward population is predominantly Negro. Forty of the 43 patients resided in the District of Columbia. Thirty-eight of the 43 patients were diagnosed during the months of May through October. The recently increased yearly incidence of cases (Fig. 1) in all likelihood reflects our increased awareness and improved case finding. In 1952 and 1953, Dr. Bessman stimulated much interest at

Children's Hospital during his study of EDTA compounds and their value in therapy of chronic lead poisoning. In June, 1955, a Lead Poisoning Clinic was established, and in all probability our case finding will continue to improve.

When a history of pica is sought in children with chronic lead poisoning, it is almost always found. In this series 40 of 43 patients had a positive history of pica although in 11 of these children pica was sought only in retrospect after other suggestive laboratory data became available. Of the 3 patients with no history of pica, the parents of 2 consistently denied any pica, while the chart of the third gave no indication that pica had been inquired about.

Twenty-one of these 43 infants and children were studied carefully by members of our psychiatry department[25] who felt that although hand-to-mouth activity is a normal phase of personality development, pica, or excessive appetite for nonedible substances, should be considered abnormal after 18 months of age. In these 21 patients the average age of onset of pica was 14 months, and the average age of initial hospitalization was 31 months. Other authors have speculated that at least 3 months must pass from the onset of pica to the onset of symptoms of lead poisoning. In this series an average of 17 months elapsed before hospital admission. Siblings of 43 per cent, and mothers of 10 per cent, of these children also had pica. It appeared that pica in these children resembled an addiction and was usually selective for a particular substance. In contrast, indiscriminate pica was seen in this series only in children with severe brain damage.

Paint, plaster, and newspaper were the materials most commonly ingested by these children, but facilities for testing lead content of these materials have not been available to us. As in other series, the paint was usually on common accessible indoor materials such as walls, woodwork, and furnishings. Lead nipple shields, imported cosmetics, and lead-painted cribs were not incriminated. The lack of appreciation of the significance of pica was most striking in several of the families in which the children were quieted and pacified by being placed beside the favorite plaster hole. The ignorance of the dangers of pica was not confined to parents and patients, for in one case a mother sought medical advice because of her child's pica and was advised to avoid conflict by permitting him to continue.

SIGNS AND SYMPTOMS

The symptoms and signs of lead poisoning observed in this series of 43 patients are summarized in Table II.

TABLE II. SYMPTOMS, SIGNS, AND DIAGNOSIS ON ADMISSION OF 43 INFANTS AND CHILDREN WITH CHRONIC LEAD POISONING

	NUMBER
Symptoms on Admission	
Gastrointestinal	27
Neurologic	22
Infection	18
Behavior problem	17
Ingestion (of any foreign material)	5
Other	4
Findings on Admission	
Infection	19
Neurologic abnormalities	17
Normal physical examination	10
Pallor	6
Vomiting	3
Allergic manifestations	2
Gum lines	0
Lead Poisoning Considered on Admission	
Yes	28
No	15

The majority of the asymptomatic group were suspected of lead poisoning by virtue of a history of pica or a report of basophilic stippling in a peripheral blood smear while the patient was being treated for an infection. Three children were first seen after ingestion of kerosene, aspirin, and furniture polish, respectively; because of a positive history of pica, further studies were carried out. One child was admitted to the hospital by the hematology service because of a chronic anemia which had been resistant to iron therapy for over a year; this child had a positive pica history. One child had a gait disturbance by history; increased metaphyseal densities on the roentgenogram aroused further interest in lead poisoning.

In the groups with symptomatic lead poisoning, symptoms were almost all referable to the gastrointestinal and central nervous systems. Gastrointestinal complaints included vomiting in 19, abdominal pain in 8, anorexia in 6, constipation in 3, and diarrhea in 2. Neurologic complaints included convulsions in 13, irritability in 10, other psychiatric or behavior disturbances in 7, and gait or walking difficulty in 4.

On the basis of physical findings these children could be separated into three major groups: those with infection as a primary problem (44 per cent), those with a variety of neurologic abnormalities (39 per cent), and those with entirely normal physical findings (23 per cent). Some of the children who were seen primarily because of infection also had neurologic abnormalities. The incidence of neurologic abnormalities observed was: convulsions in 8, coma in 5, marked irritability in 4, positive Babinski sign in 4, nuchal rigidity in 3, nystagmus in 2, lethargy in 2, hemiplegia in 2, optic neuritis in 2, and abducens nerve palsy, aphasia, spastic paraplegia, spastic extremity, central deafness, and intraocular ophthalmoplegia in 1 each. Six of the 43 children had marked pallor on admission which focused attention on the hematopoietic system. An observation that deserves particular emphasis was the absence of lead lines on the gums in all patients.

LABORATORY DATA

A summary of the pertinent laboratory findings is presented in Table III. Undoubtedly the two most helpful diagnostic procedures, other than lead determinations, were hematologic and roentgenographic studies. Hematologic studies on admission were abnormal in 37 of the 43 patients. The most common abnormalities were anemia (below 10 Gm. of hemoglobin) in 35 children, basophilic stippling in 29, and eosinophilia (above 5 per cent) in 23. Although hemolytic crises have been described, all of the patients with anemia appeared to have the typical peripheral blood smears and indices of iron deficiency. Punctate basophilia deserves comment. Not all children with lead poisoning showed stippled red cells; of those who did, one-third showed stippling only after repeated smears were examined. Obviously, it is of considerable assistance to have a properly stained and prepared blood smear, an unhurried microscopic examination by a trained observer, and the verbal or written statement from the clinician to the laboratory regarding the possibility of lead poisoning. It was striking that eosinophilia was

present in this series in 23 patients on at least one smear during hospitalization. Two children with eosinophilia had allergic histories, and two had stools containing ova and parasites. The remainder of these patients were not carefully studied in this respect. One might speculate on the possibility that these children with pica might also have ingested dirt which contained ova. The leukocytosis present in 13 patients was associated with infection, and did not correlate with severity of lead intoxication.

TABLE III. LABORATORY DATA OF 43 INFANTS AND CHILDREN WITH CHRONIC LEAD POISONING

	NUMBER	
I. Hematology		
Normal (on admission)		6
Abnormal (on admission)		37
Anemia moderate (8-10 Gm. Hb/100 ml.)	19	
Anemia severe (below 8 Gm. Hb/100 ml.)	16	
Leukocytosis (above 15,000/mm.^{3})	13	
Basophilic stippling—		
First Smear	20	
later smears only	9	
Eosinophilia and/or stippling	33	
II. Urine		
Normal		28
Abnormal		15
Proteinuria	8	
Glucosuria	5	
Pyuria	8	
Hematuria	2	
III. Blood Sugar		
Normal		2
Elevated		5
IV. Spinal Fluid		
Normal		10
Abnormal		16
Protein increased	15	
Cells increased	9	
Sugar increased	3	
Pressure increased (Pressure normal—3)	4	
V. Electroencephalogram		
Normal (No encephalitis)		10
Abnormal		
(All encephalitis)		7
Focal	3	
General	4	
VI. X-ray Study		
Long bone		37
Normal	3	
Abnormal	34	
Skull		10
Normal	6	
Abnormal	4	
Abdominal flat plate		3
Normal	0	
Abnormal (all encephalitis)	3	

Urinalyses were abnormal in slightly over one-third of the group, but the majority of specimens were collected after use of indwelling plastic catheters. Glucosuria was present in 5 children.

A variety of blood chemistry tests was performed, but not in a significant number of patients. Five of 7 children tested demonstrated elevated blood sugar levels. In this regard one child had 11 urine tests positive for sugar and 3 of 10 blood sugar determinations were elevated (300 mg. per 100 ml., 165 mg. per 100 ml., and 255 mg. per 100 ml.). In this child a trial dose of insulin produced a series of convulsions and coma.

Abnormal spinal fluid findings occurred primarily in the group with encephalitis, and spinal fluid was obtained after onset of convulsions or coma. In some cases the spinal fluid abnormalities caused confusion as to possible aseptic meningitis or encephalitis of viral or fungal etiology. Of the 17 patients with clinical evidence of encephalopathy, 12 had abnormal spinal fluid findings, 4 had normal spinal fluid findings, and 1 was not tested. The remaining 4 patients with abnormal spinal fluid all had clinical lead intoxication without neurologic signs or symptoms.

Electroencephalograms were performed in a minority of the patients.

In 7 patients, who clinically were considered to have lead encephalitis, there were focal or general abnormalities on the electroencephalogram. In none of the 10 patients designated as "asymptomatic" or "simple lead intoxication" was there any electroencephalographic abnormality.

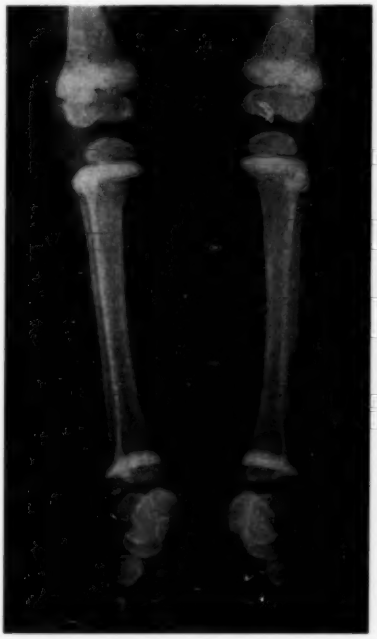

Fig. 2.—X-rays of the lower extremities of a patient with chronic lead poisoning, showing the increased densities at the metaphyses.

Roentgenographic studies, as mentioned previously, were of considerable assistance in establishing a working diagnosis. Increased metaphyseal densities can be seen in any of a variety of other diseases which cause a retardation of bone growth. Nevertheless, 34 of 37 long bone roentgenograms were interpreted as suggestive of heavy metal poisoning (Fig. 2). In this study, one chest roentgenogram, one pelvic roentgenogram (Fig. 3), and 4 skull roentgenograms demonstrated lines of increased density. In 3 children the presenting symptoms of vomiting, abdominal pain, or abdominal distention suggested a possible acute intestinal obstruction, but abdominal roentgenography revealed no evidence of obstruction. However,

Fig. 3.—X-ray of the pelvis of a patient with chronic lead poisoning showing increased density of Ilian casts and ischia. Also note the density of the distal end of the right twelfth rib.

flecks of radiopaque material seen were felt to be fragments of lead-containing material (Fig. 4).

For the purpose of this study, a pretreatment blood lead level was considered suspicious in the range of 0.06 to 0.08 mg. per 100 ml., and toxic above this concentration; a pretreatment urine lead level was suspicious in the range of 0.07 to 0.15 mg. per liter per 24 hours, and toxic above

this range. Prior to treatment, 10 of 13 children tested had suspicious or toxic blood lead levels, and 15 of 20 children tested had suspicious or toxic urine lead levels. Only 5 of these 25 abnormal specimens were obtained from patients with encephalitis; this was because the first blood or urine sample from the majority of encephalitic patients was collected after EDTA therapy had already been instituted.

Fig. 4.—X-ray of the abdomen of a patient with chronic lead poisoning showing flecks of lead-containing material (paint) along the course of the intestines (arrows).

It has previously been observed that the level of lead in the blood or urine does not correlate well with the clinical picture, and such was our experience in this study. It had been thought that the first sample of blood or urine collected after the start of EDTA therapy might show a better correlation with the clinical picture, but this was not so (Table IV).

DIFFERENTIAL DIAGNOSES

Chronic lead poisoning was considered as a preliminary diagnosis in 28 of the 43 patients (65 per cent). Lead intoxication, like syphilis, sickle-cell disease, and infectious mononucleosis, can affect many systems and mimic many diseases. To illustrate this potential confusion in diagnosis, several examples might be offered. Three children were first thought to

TABLE IV. BLOOD AND URINE LEAD LEVELS BEFORE AND AFTER EDTA THERAPY OF CHRONIC LEAD POISONING

Blood Lead Levels
(mg./100 ml.)

	BEFORE EDTA THERAPY			DURING FIRST 24 HOURS OF EDTA THERAPY		
	0.02-0.06	0.06-0.08	>0.08	0.8-1.2	1.2-1.6	>1.6
Asymptomatic	1		3			1
Simple intoxication	1	1	2			1
Mild encephalitis		2	1		1	1
Severe encephalitis	1		1	1		2

Urine Lead Levels
(mg./L./24 hr.)

	BEFORE EDTA THERAPY				DURING FIRST 24 HOURS OF EDTA THERAPY			
	<0.07	0.07-0.15	>0.15	<0.7	0.7-1.5	1.5-2.2	2.2-3.0	>3.0
Asymptomatic	2	3	4		1	3	1	1
Simple intoxication	3	2	3	3		1	1	1
Mild encephalitis			2		2	1		1
Severe encephalitis			1	3		2		

have acute abdominal disease with possible intestinal obstruction; one child had a resistant anemia; one was treated as a diabetic. Poliomyelitis was diagnosed in another child with a spastic paraplegia resulting from chronic intoxication. It is of interest that children differ from adults with chronic plumbism in that the child's lower extremities are more commonly affected than his upper extremities.

MORTALITY AND PATHOLOGY

Three children (7 per cent) died (all with severe encephalopathy) after an average of 2⅓ days of hospitalization. Gross pathological diagnoses on one of these children[13] were edema and congestion of the brain, hepatic failure, pulmonary hemorrhage, and ascariasis. There were gross and/or microscopic changes in the liver, kidneys, and brain. Chemical analysis in this single case revealed the following lead concentrations (in milligrams per 100 grams of tissue): bone 9.96, kidney 0.8, liver 0.78, lung 0.10, brain 0.00. This reflects the previously noted poor correlation between clinical lead encephalopathy and chemical analysis of brain tissue. In the presence of marked anemia, the bone marrow of 2 children demonstrated marked erythroid hyperplasia.

THERAPY

This group of patients with chronic lead poisoning was treated with EDTA. No BAL was used. EDTA was given either intravenously or subcutaneously in the standard dosage of 30 mg. per kilogram per day; in the first 18 cases 0.5 Gm. was given 3 times daily regardless of weight. EDTA was given for 5 days, discontinued for 3 days, and then repeated for 5 days. In the present series no evidence of local or systemic toxicity from EDTA has been noted. In general, treatment has been dictated by the clinical status of the individual since the results of the chemical studies for lead were usually not reported for 1 to 2 weeks and then frequently did not correlate well with the severity of the symptoms. The most critical problem in therapy is the management of the child with lead encephalopathy who is in status epilepticus or coma. Craniotomy and reduction of spinal fluid pressure by repeated lumbar puncture have not been used consistently in our patients and we have too few data on which to base conclusions as to their efficacy. Intensive supportive nursing care, parenteral anticonvulsants, restricted parenteral fluids, and parenteral EDTA have been the mainstays of therapy. Oral EDTA has not been used in recent years because preliminary work showed very little promise.

CASE FOLLOW-UP

Follow-up of this group of patients is shown in Table V. It is important to note that one-fourth of the patients have been lost to follow-up. The persistence of pica, which would seem the crux of the problem, has unfortunately not been adequately followed, although our lead clinic is vigorously pursuing this problem now. In light of the thought that the severe neurologic residuals of lead encephalopathy might be due to repeated or continued poisoning, our series may be significant in that only 1 of 43 children went to a convalescent or lead-free home on discharge from the hospital. The other children returned to their parents and previous environments. It would

seem that safer housing for the entire family would be more feasible than the use of convalescent homes in preventing recurrent plumbism. This, of course, brings the problem into the realm of public health, sociology, and the law. We have seen recently that our social worker has been able to give affected families effective help in finding more satisfactory housing.

techniques.[35] As a result of those evaluations, the children were classified as having severe, moderate or no organic psychiatric residuals. It was the consensus of these workers that psychologic testing was the most efficient method of assessing mild to moderate degrees of organic brain damage. Three children were not tested psychologically, and on the basis

TABLE V. FOLLOW-UP OF 43 PATIENTS WITH CHRONIC LEAD POISONING

	ASYMPTOMATIC	CLINICAL SYMPTOMS NO ENCEPHALITIS	ENCEPHALITIS		TOTAL
			MILD	SEVERE	
Death	0	0	0	3	3
No follow-up	4	5	2	0	11
Follow-up	8	9	6	6	29
Pica continued	2	2	2	3	9
Pica stopped	1	4	2	1	8
Pica unknown	5	3	2	2	12
Well	5	8	3	0	16
Moderate residual	3	1	0	1	5
Severe residual	0	0	3	5	8

In this series of 43 patients, 3 children died and at least 13 others have moderate or severe neurologic and/or psychologic residuals. Of the group of 17 children with encephalitis, 2 have not been followed, 3 are well, 9 have moderate or severe residuals, and 3 are dead. Forty-five per cent of the 29 children who survived and were followed up show residuals. This is a far grimmer picture than that painted by other recent reports[2, 5, 7, 8, 10, 19] and merits further study. The use of psychologic studies in this series may, perhaps, account for a part of the difference.

A group of 21 children who had recovered from lead intoxication were evaluated here on the basis of interviews with the parents, playroom sessions with the child, and by psychologic testing in the realms of intelligence, social maturity, and projective

of other studies it could not be determined whether they had no residuals or moderate residuals. Of the remaining 18 children, 8 had had encephalitis, and all had residuals (1 moderate and 7 severe). Of the 10 children who had had lead poisoning without encephalitis, 5 had moderate residuals and 5 had none. It is impossible, of course, to be certain how much of this brain damage is a result of the lead poisoning and how much may have preceded it. We know that one child was definitely retarded before the onset of his lead poisoning; 3 others had histories compatible with possible pre-existing damage, e.g., traumatic premature birth or bizarre autistic-type behavior. All 4 of these children fell into the group with severe residuals. Nevertheless, the residual morbidity resulting directly from chronic lead poisoning is truly shocking. The

variation between our results and those in the literature may suggest any of the following: (1) a difference in the population studied, (2) significant difference in therapy, (3) difference in the measuring devices and norms in the follow-up of these children, or (4) a combination of all these factors. We feel that the third alternative is the most plausible in the problem of plumbism.

The Lead Poisoning Clinic, which was established as a result of interest at this hospital in the problem of plumbism, is staffed by a team consisting of a pediatrician, a pediatric resident, a psychiatrist, a psychologist, and a social worker. The clinic provides a means of screening all pica cases, of standardizing in-patient therapy, and of better following patients discharged after treatment. When necessary, psychiatric assistance has been offered with greater parental acceptance of the team approach than of direct psychiatric referral alone. With psychiatric help, many of the parents are better able to handle their children's needs, and as the pica of these children becomes less of a problem, their lead intoxication tends to disappear.

SUMMARY AND CONCLUSIONS

The experience at Children's Hospital in the management of 43 children with chronic lead poisoning over a 7-year period is presented. The observed mortality of 7 per cent in 43 patients is significantly high even though it is an improvement over that noted in many previous reports. More important, the 45 per cent incidence of neurologic and psychiatric residual morbidity deserves serious consideration and further study. Chronic lead poisoning has become an increasingly significant problem as awareness of the diagnosis, treatment, and residuals has increased. Because lead encephalitis is an important killer and crippler of children, early diagnosis and therapy (with EDTA), as well as adequate and continued follow-up, are essential. The simple expedient of routine inquiry into the presence of pica will bring to light many cases of plumbism before they become symptomatic. Furthermore, counseling directed at cessation of pica seems to be an effective tool in prevention of continued lead poisoning. Perhaps even more important are the roles of the private physicians, public health authorities, and lawmakers in preventing the occurrence of this dangerous disease through education of the public, inspection and proper repair of substandard housing, and more stringent laws regarding lead-containing paints.

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HEMANGIOMA WITH THROMBOCYTOPENIA

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HEMANGIOMA with associated thrombocytopenia is a relatively rare occurrence. The purpose of this paper is to review fourteen cases in which these two entities were observed. Nine of these, Table II cases 1 to 9, are from various reports in the literature, and five (two of which, Table II cases 10 and 11, were previously reported) are from the Pediatric and Mixed Tumor Service of Memorial Cancer Center. This is the initial report of the following three cases.

CASE REPORTS

CASE 1.—H. P. was a 5-week-old white girl who was delivered spontaneously at term, at which time she showed multiple hemangiomata. Because of profuse bleeding from the slightest trauma, she was admitted to Memorial Hospital on Dec. 10, 1941.

On admission physical examination revealed an immature-looking child weighing 6 pounds, 9 ounces. Numerous firm, compressible hemangiomatous nodules were present over the scalp, extremities, chest, back, abdominal wall, around the genitalia, fingers, back of the ears, and under the tongue (Fig. 1). Some of the larger lesions had ulcerated and were bleeding. The liver and the spleen were greatly enlarged and felt nodular to palpation. The heart and lungs were clear.

The platelet count was 68,000 per cubic millimeter of blood.

Roentgenograms of the bones showed several punched-out areas.

One of the tumors, taken out at another institution, showed not only angioma, but also a center in which there were islands of blood cell formation with presence of megakaryocytes. The diagnosis of multiple congenital hemangiomas containing blood islands was made.

The parents refused therapy beyond a single blood transfusion, and she was discharged "against advice" sixteen days after admission. She died at home at the age of 3 months.

CASE 2.—M. B. was a 2-year-old white girl who was delivered normally at full term and developed normally. Her personal and family history were noncontributory.

At the age of 18 months, after a fall, she was noticed to have a swelling over the left clavicle and scapula which, on x-ray, was diagnosed as cortical hyperostosis. Four months later she began to manifest excessive bruising. An initial platelet count, done after this was noted, was 60,000 per cubic millimeter. A diagnosis of idiopathic thrombocytopenic purpura was made by her physicians, and the child was given 150 mg. of cortisone daily. After two weeks on this therapy, the bleeding tendency increased, and hospitalization became necessary.

On Dec. 23, 1953, splenectomy was performed in a hospital in her community. The spleen appeared normal in size and texture, and no accessory splenic tissue was found.

Following surgery, she had a stormy course requiring daily direct

From the Pediatric and Mixed Tumor Services of Memorial Center for Cancer and Allied Diseases.

transfusions for the control of bleeding. She had an episode of a convulsion followed by a transient right-sided hemiplegia and aphasia. She also developed a septicemia which was finally controlled by antibiotics.

Gradually, her bleeding subsided; but no improvement in the platelet count was noted. At the time of discharge, the platelet count was 23,000 per cubic millimeter.

On Feb. 4, 1954, because of continued increase in the size and extent of the soft tissue swelling about the left shoulder and continuing signs of cutaneous purpura, she was referred

Fig. 1.—H. P., female, aged 5 weeks. Superficial bleb-like hemangiomas on right arm and vulva; subcutaneous nodules on anterior thoracic and abdominal walls. The liver and spleen were palpable to the level of the umbilicus.

Fig. 2.—M. B., female, aged 2 years. Swelling and engorged blood vessels over the left shoulder girdle from a diffuse subcutaneous hypertrophic hemangioma which had no cutaneous component.

to Dr. George Pack for further treatment at Memorial Cancer Center.

On admission, physical examination showed a "moon-faced" little girl of 2 years, with very hairy eyebrows, a shower of fine petechiae over her entire body, and ecchymoses on the legs. There was an area of fullness around the left pectoral girdle, especially over the scapula and in the axilla (Fig. 2). There was prominence of veins around the whole tumefaction. No bruit was heard. The mass was diffuse and firm to palpation. There was a transverse scar on the left upper abdominal area. The liver was palpable 1 cm. below the right costal margin. The rest of the physical examination was not revealing.

The platelet count was 21,000 per cubic millimeter of blood. The rest of the hemogram was normal. The bone marrow showed an increase in megakaryocytes.

A review of the submitted x-ray films revealed findings consistent with the clinical impression of a vascular or soft-part tumor, with slight compression changes in the left first, second, and third ribs.

The patient was started on hydrocortisone, 25 mg. daily, and this was maintained for 7 weeks. She was put on a diet free from milk and eggs and their products. This elimination diet was maintained throughout her hospital stay.

A regimen of vitamins including vitamins C and B_{12} was also instituted.

Within a few weeks the hemorrhagic tendency was noted to have diminished, and the platelet count began to rise significantly. The tumor, to most observers, diminished slightly in size.

After a sustained platelet count over 100,000 per cubic millimeter for 28 days, the left axillary region was explored and biopsied. The pathologic report was hypertrophic hemangioma.

The postoperative course was uncomplicated. The patient was discharged one week after the operation, at which time she had a normal platelet count.

A subsequent report on her, dated Sept. 26, 1955, 17 months after discharge, revealed that she was doing well. Her hemogram, including platelet count, was normal. The tumor mass had almost completely disappeared.

CASE 3.—J. B. was a 1-month-old white boy (Fig. 3) admitted to Memorial Center on Nov. 12, 1954. He was delivered by cesarean section at full term, at which time a large purplish mass was noted on his left thigh. The neonatal course was uneventful until 3 days prior to admission when he manifested increased irritability, pallor, and poor feeding. A swelling was noticed on the left leg distal to the lesion.

Physical examination showed a well-developed, fairly well-nourished, but pale 1-month-old infant, with a large purplish, raised, firm, shiny mass on the left thigh which measured 12 by 10 cm. No bruit was heard over the tumor. There was pitting edema distal to the thigh, and numerous petechiae over the left thigh and upper portion of the leg. The rest of the physical examination was not revealing.

Laboratory examinations on admission showed a platelet count of 3,000 per cubic millimeter; a hemoglobin of 4.3 Gm.; and a red blood cell count of 1.5 million. Serum bilirubin was 3.70 mg. per 100 c.c. The other laboratory examinations, including x-rays, were not remarkable.

Immediately following admission, because of marked anemia, the patient was given small transfusions of whole blood. On the fourth day, an aspiration biopsy of the tumor was performed, and this was reported as "angioma."

He was subsequently put on an elimination diet free from milk and eggs and their products. A regimen of vitamins including vitamins C and B_{12} was also instituted.

Because of persistent and marked thrombopenia, cortisone was started.

Fig. 3.—*A*, J. B., male, aged 1 year. Hypertrophic hemangioma completely involving anterior and lateral aspects of the left thigh. It measured 23.5 by 16.5 cm. (54 cm. at its widest diameter) at this time. *B*, Same child at 16 months of age. The tumor has begun to regress and measures 48 cm. at its widest diameter. *C*, Same child, aged 3 years, 3 months. Further regression of tumor.

Seventy-five milligrams daily was given for a month, with some increase in the platelet count (5,000 to 15,000), and disappearance of the purpura. At that time, he required transfusions less frequently (once every two weeks). The tumor, meanwhile, continued to increase in size.

One month after admission, the spleen was felt for the first time to be 2 cm. below the left costal margin. The course in the hospital was complicated by a very severe homologous serum jaundice which lasted for three months. He showed an increasing hepatosplenomegaly, and an elevated serum bilirubin which reached 35 mg./100 c.c. at its peak. During the course of this complication, the patient lost a pound, and did not gain any weight for four months.

He was discharged after 7 months, still with a low platelet count ranging from 10,000 to 20,000. At this time, the skin over the tumor had so thickened that danger of bleeding from the tumor with the slightest trauma was less imminent, although the tumor still continued to increase in size.

In the outpatient department follow-up, he continued to require blood transfusions 3 to 4 times a month.

Three months after discharge, he was readmitted because of the persistently enlarging tumor which had several ulcerations and bleeding points. On Sept. 16, 1955, a femoral arteriogram and insertion of radon gold seeds was performed under general anesthesia without complications. A total of 19.9 mc. in 31 seeds was inserted. He was discharged in 5 days.

He required no transfusions during the following 5 months, and his hemoglobin remained at 9.5 to 13 Gm.

The tumor continued to increase in size until 3 months after the insertion of the radon gold seeds, when it was noticed to be smaller for the first time. At the same time, there was significant increase in the platelet count from 20,000 to 134,000 per cubic millimeter. From then on, the tumor progressively decreased in size, and the platelet count has risen to a normal level.

Table I shows a résumé of the 5 cases seen in Memorial Cancer Center, their treatments, and the effects of same.

The nine instances of hemangioma and purpura we have been able to find in the American literature and the 5 Memorial Center cases have been tabulated in Table II. Comparisons of the findings and the course of each reveals the following data.

TABLE I. RÉSUMÉ OF THE FIVE CASES SEEN IN MEMORIAL CANCER CENTER

CASE NUMBER	SEX	TREATMENT	EARLY EFFECTS		LATE EFFECTS	
			HEMANGIOMA	THROMBOPENIA	HEMANGIOMA	PERSISTENT THROMBOPENIA (MONTHS)
1*	M	Splenectomy	0	0	Decreased	Over 6
2*	F	Expectant + 300 r.	0	0	Decreased	Over 5
3	F	(a) Cortisone; splenectomy	Enlarged	0	—	Over 3
		(b) Hydrocortisone; diet	0	Under 6 weeks	Decreased	
4	M	(a) Hydrocortisone; diet	0	0	Enlarged	Unaltered (no purpura in 6 months)
		(b) Radon seeds	0	0	Decreased (after 3 months)	Over 3
5	F	Refused	0 Death	0		

*Previously reported by Weissman and Tagnon.[11]

TABLE II

CASE NUMBER	AGE	SEX	HEMANGIOMA		AGE (FIRST OBSERVED)	PURPURA (FIRST OBSERVED)	BLOOD	
			VARIETY	SITE			THROMBOPENIA	ANEMIA
1 Kasabach and Merritt[2]	2 mo.	M	Capillary	Left thigh	At birth	2 mo.	+	+
2 Bogin and Thurmond[5]	6 wk.	M	No biopsy	Thoracic wall	At birth	6 wk.	+	+
3 Silver and co-workers[4]	14½ mo.	F	Capillary Cavernous	Scalp Back	At birth 5 mo.	18-20 mo.	+	+
4 Rhodes and Borelli[1]	6 mo.	M	Hemangioendothelioma	Neck and thorax	At birth	2 mo.	+	+
5 Southard and co-workers[12]	21 days	F	Capillary	Left leg	At birth	5 days or earlier	+	+
6 Good and co-workers[13]	8 wk.	M	Hemangioendothelioma	Face and neck	2 wk.	4 wk.	+	+
7 Good and co-workers[13]	5 mo.	F	Capillary	Left leg	At birth	3-5 mo.	+	+
8 Good and co-workers[13]	3½ mo.	M	Capillary; cavernous	Left axilla	2 mo.	2-3 mo.	+	+
9 Meeks and co-workers[14]	1 mo.	M	No biopsy	Right deltoid	At birth	2 wk.	+	+
10 Memorial	9 mo.	M	Hypertrophic	Right arm	At birth	9 mo.	+	
11 Memorial	3 mo.	F	Hypertrophic with mitotic figures	Left arm	At birth (bluish arm); 1 wk. (enlarged)	2 mo.	+	

Data on cases 10 to 14 are amplifications of the same cases (Nos. 1 to 5) in Table I.

TABLE II

BLEEDING TIME	CLOTTING TIME	MARROW	SPLEEN	THERAPY	COMMENT
11	1	—	Not stated	Supportive; x-ray; radium to tumor	Reduction in tumor size 5-6 wk. Thrombopenia improved 3 mo. after radiotherapy started
5	11	Poor thrombocyte formation	Not palpable	Supportive; radium to tumor; x-ray to spleen; splenectomy	Anemia improved postoperatively. No appreciable reduction in tumor size 4 wk. postoperatively. Thrombopenia persisted for over 4 mo. post-splenectomy
5	20	Hyperplastic; megakaryocytes increased	2 cm.	X-ray to tumor initially, then supportive	Temperature regression from initial radiotherapy, but subsequent recurrence and hemorrhage terminating fatally
4	25	—	1 finger-breadths	X-ray to tumor (2 courses); supportive	Tumor enlarged after first course and persisted; thrombopenia for 5 mo.
60	30	"No pathology"	Not stated	X-ray to tumor; supportive	Platelets rose 1 wk. after starting radiotherapy. Tumor size diminished 3 wk. from beginning therapy
3	6	Increased megakaryocytes; shift to left	Not palpable	Splenectomy; supportive	Thrombopenia persisted, but tumor diminished in size 4 mo. post-splenectomy. Died 5 mo. post-splenectomy from fulminating infection
—	10	Increased megakaryocytes; shift to left	At costal margin	Supportive; splenectomy; irradiation; excision	Stormy postoperative course. Thrombopenia present 3 mo. postoperatively. Bleeding in tumor 3 mo. post-irradiation; no thrombopenia. Bleeding in tumor area at intervals for 2 years after excision
3	15	Increased megakaryocytes; shift to left	Not palpable	Supportive; irradiation; ACTH	Thrombopenia ceased 2½ mo. after start of irradiation; improved slightly on ACTH; tumor regressed well
—	20	Megakaryocytes conspicuous	3 finger-breadths	Supportive; irradiation; cortisone; splenectomy	Tumor increased in size during irradiation; spleen also increased in size. Platelet count normal 5 days after operation. Shrinkage of tumefaction dramatic and coincided with normal platelet count
7	11	Hypocellular megakaryocytes not seen	Not palpable	Supportive; splenectomy	Thrombopenia persisted for over 6 mo. post-splenectomy
5½	9½	Normal	Not palpable	X-ray to tumor (300 r.); antibiotics	Thrombopenia terminated 5 mo. after onset of clinical signs. Was infection associated with hemorrhage or sclerosis?

TABLE II—(

CASE NUMBER	AGE	SEX	HEMANGIOMA		AGE (FIRST OBSERVED)	PURPURA (FIRST OBSERVED)	BLOOD	
			VARIETY	SITE			THROMBOPENIA	ANEMIA
12 Memorial	5 wk.	F	Angioma with erythropoietic centers	Multiple	At birth	At birth	+	+
13 Memorial	18 mo.	F	Hypertrophic	Left axilla, thorax, and supraclavicular area	18 mo.	18 mo.	+	+
14 Memorial	1 mo.	M	Hypertrophic	Left thigh	At birth	1 mo.	+	+

Fig. 4.—*A*, R. H., male, aged 9 months (Case No. 10, Table II). Diffuse hypertrophic hemangioma of the upper-half, right forearm. Splenectomy was performed, but the thrombopenia persisted for 6 months following the operation. *B*, Same child, 4 years of age. There has been excellent regression of the mass.

II—CONT'D

BLEEDING TIME	CLOTTING TIME	MARROW	SPLEEN	THERAPY	COMMENT
—	—	—	Very large or mass(?)	Supportive	Died at age 3 mo.
11	1	Normal; megakaryocytes increased	Normal	Cortisone; splenectomy; high vitamin and elimination diet; hydrocortone	No response to initial treatment and splenectomy. Massive hemorrhage and hemiplegia post-splenectomy. Normal platelet count 8 wk. after this regime of treatment
8	15	Normal	4 cm.	Cortisone; high vitamin and elimination diet Radium	Purpura ceased 2 mo. after this first therapeutic regimen. Tumor continued to enlarge; thrombopenia persisted Tumor diminished in size and platelet count increased gradually to normal 3 mo. after this treatment

A.

B.

Fig. 5.—*A*, M. S., female, aged 3 months (Case 2, Table II). Hypertrophic hemangioma involving almost the entire left arm. This was treated with a small dose of radiotherapy (300 r.). *B*, Same child, aged 3½ years. The mass has regressed. There is some thickening of the skin and the subcutaneous tissues.

OBSERVATIONS

1. In all these patients the tumor masses were observed either at birth or early infancy, with the exception of one case, Table II case 13, where the hemangioma was noted at the age of 18 months.

2. Thirteen cases showed cutaneous evidence of hemangioma. One patient[12] never showed any cutaneous component of the tumor. The identity of the tumor was not established until biopsy was performed 9 months after the onset of the illness.

3. Splenectomy was performed in 6 of the 13 treated cases. In one, Table II case 9, a satisfactory effect on the thrombopenia and tumor was noted within 1 week after the operation. In the other 5 cases the thrombopenia persisted from 3 to 5 months. The serious operative and postoperative problems which sometimes occur were dramatically illustrated by the hemiplegia which occurred in one of our patients, and the acute fulminating infection that led to the demise of a patient reported by Good and his colleagues, Table II case 6.

4. Steroids were used in 4 patients. There was cessation of purpura in one patient, in spite of persistence of the thrombopenia. There was slight improvement of the thrombopenia in another. The former was on an elimination diet also.

5. Irradiation or radium treatments were used in 10 cases. It proved to be of value in 7 cases, Table II cases 1, 5, 7, 9, 11, and 14. In one, Table II case 3, there was only temporary regression of the tumor.

DISCUSSION

In a study of 526 infants under 1 year of age, Bivings[7] found the incidence of "strawberry" (capillary) hemangiomas to be 8.7 per cent. Thrombocytopenic purpura is not an unusual condition in children. The simultaneous occurrence of these two entities may, therefore, be simply coincidental. However, in all these reported cases, the thrombocytopenia subsided at the same time as, or subsequent to, the regression of the tumor mass. This seems to suggess that the occurrence of the two phenomena might be a definite clinical syndrome. Various explanations have been offered to support the possible relationship of the two events, none of which are satisfactory.

Silver and associates advanced three conflicting theories to explain the low platelet count in thrombopenic purpura: (1) increased phagocytosis of the platelets by the reticuloendothelial tissues; (2) increased utilization of platelets in an attempt to repair multiple capillary defects; and (3) decreased production of platelets by the megakaryocytes in the bone marrow. They state, in their case report, that the presence of a widespread capillary defect might suggest increased utilization of platelets as the cause of the thrombocytopenia.

Good and his associates considered that sequestrations, utilization, and destruction of platelets occur within the tumor as evidenced by the presence of platelet thrombi in sections of the tumors on biopsy, surgery, and necropsy. One of our patients showed islands of blood cell formation with the presence of megakaryocytes in the tumor.

Whether there is a single basic hematopoietic defect which in fetal

life results in the production of angiomas and, subsequently, is manifested by thrombopenia, is a consideration which belongs to the realm of pure speculation. It could be assumed, however, that irrespective of the validity of the evidences of a relationship, the very presence of a growing, bleeding angiomatous mass would produce a constant and perhaps excessive local demand for platelet mobilization. The cost of this mobilization might be the deprivation of platelets in other anatomic sites, with consequent purpura.

SUMMARY AND CONCLUSIONS

Fourteen cases of hemangiomas in children with associated thrombocytopenic purpura are reviewed, five of which were treated by us.

Splenectomy was not effective on the thrombocytopenia except in 1 of the 6 cases in which it was performed. The serious operative and postoperative risks are related.

Irradiation or radium therapy proved to be of value in 7 of the 10 cases in which it was used.

Subsidence of the thrombocytopenia always coincided with, or followed, regression of the tumor mass. Attempts to explain this relationship are reviewed. Utilization and destruction of platelets in the tumor mass is the most likely explanation.

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THE SELENIUM CONCENTRATION IN PLACENTAL TISSUE AND FETAL CORD BLOOD

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THE findings of epidemiological studies, conducted among Oregon children in recent years, revealed that the trace element selenium may be responsible for rendering the teeth more susceptible to dental caries attack.[1, 2] For further knowledge on this subject, a study was conducted for the purpose of determining the selenium content of enamel and dentine of different groups of teeth. The results showed that the selenium content of primary teeth was higher than that of the permanent.[3] In view of this it was thought advisable to investigate the role of the placenta in selenium metabolism.

METHODS AND RESULTS

For the purpose of this investigation, samples of placental tissue and fetal cord blood were obtained from normal patients at the county hospital.*

For the determination of selenium concentration, the samples were subjected to a routine wet ashing with nitric acid, using 25 ml. of sulfuric acid as solvent. Each sample was diluted with 50 ml. of 6 M hydrochloric acid and the selenium precipitated with SO_2 and hydroxylamine. The selenium was redissolved and the quantity determined spectrophotometrically by the method of Cheng.[4]

Altogether, 13 placental tissue samples and the 13 corresponding fetal cord blood samples were analyzed for selenium. The distribution of selenium concentration in placental tissue and fetal cord blood is presented in Table I. All of the specimens contained selenium in varying amounts. The average selenium concentration for the placental tissue was 0.18 ppm. and that for the fetal cord blood, 0.12 ppm.

DISCUSSION

The placental transmission of selenium has been investigated in laboratory animals. It was demonstrated that in rats and cats selenium is transmitted to the fetus through the placenta, whether it is incorporated in the diet as organic or inorganic selenium. In the animals fed organic selenium, however, more of this element was stored in the fetus.[5] The passage of selenium through the mammary gland into the milk has been demonstrated in cows of seleniferous areas of the country,[6] and also in rats injected with subtoxic amounts of radioselenium.[7]

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*The samples were collected through the courtesy of Dr. Ralph C. Benson, Professor and Head, Department of Obstetrics and Gynecology, University of Oregon Medical School.

It is believed that the findings of the present study provide the first evidence of placental transmission of selenium in the human being. From the mean values shown in Table I, it appears that a close association exists between the selenium values of placental tissue and fetal cord blood. On the basis of this, the suggestion is advanced that the placenta may act as an organ of accumulation and transfer of selenium rather than a barrier for preventing amounts of this element, which may be considered harmful, from reaching the fetus.

TABLE I. DISTRIBUTION OF SELENIUM CONCENTRATION IN PLACENTAL TISSUE AND FETAL CORD BLOOD

SELENIUM IN PPM.	NUMBER OF CASES	
	PLACENTA	BLOOD
0.07-0.09	–	3
0.10-0.12	–	3
0.13-0.15	3	6
0.16-0.18	3	1
0.19-0.21	6	–
0.22-0.24	1	–
	Mean 0.18 ± 0.007*	Mean 0.12 ± 0.008*

*Standard error of the mean.

At the present time, no adequate information is available regarding human beings' daily ingestion of small amounts of selenium that may be tolerated without ill effects. Most of the selenium ingested is known to be eliminated mainly through the urine. As a result of this, determination of urinary selenium concentration is a good indicator of selenium intake.[8] However, on the basis of our present knowledge the values reported in this study for the placental tissue and fetal cord blood are regarded as being of considerable interest, particularly since the subjects of our investigation did not live in a known seleniferous area of the country.[9]

The results of our study seem to suggest that a dissimilarity exists in the role of placenta in selenium and fluoride metabolism. It is known that the fluoride content of primary teeth is lower than that of the permanent.[10] Furthermore, occurrence of mottled enamel in primary teeth is a rare phenomenon, except when the water supply contains extremely high amounts of fluorine.[11] However, the results of a number of studies with human beings and laboratory animals, recently summarized,[12] have not yet provided an adequate explanation as to the exact function of the placenta in the metabolism of fluorides.

The relationship between the fluoride concentration in placental tissue and fetal cord blood was investigated in two groups of subjects living in areas where the public water supply did not contain any appreciable amounts of fluorine.[13] In the first group the average fluoride concentration in placental tissue was found to be 101 μg/100 Gm., and that in cord blood, 17 μg/100 ml., a ratio of 5.9. In the second group of subjects the average fluoride concentration in placental tissue was 67 μg/100 Gm., and that of cord blood, 22 μg/100 ml., a ratio of 3.0. In contrast, the ratio in our study between the average selenium concentration in placental tissue and fetal cord blood was only 1.5.

It thus appears that the level of placental transmission of selenium may be responsible for the higher content of this trace element found in the primary teeth in comparison with that of the permanent teeth.

In view of our findings, it would be particularly interesting to investigate the selenium content of placental tissue and fetal cord blood as well as to determine the selenium concentration in primary and permanent teeth among persons living in known seleniferous areas of the country.

SUMMARY

The concentration of selenium in placental tissue and fetal cord blood of normal patients was determined.

The average selenium concentration in placental tissue was 0.18 ppm. and that in fetal cord blood, 0.12 ppm. The results indicate a close association between the selenium values of placenta and fetal cord blood.

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A DISTURBANCE OF CARBOHYDRATE METABOLISM CAUSED BY LESIONS OF THE CENTRAL NERVOUS SYSTEM

Report of a Case in a Child With a Hypothalamic Tumor and Review of the Clinical Reports in the Literature

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GLYCOSURIA may occur in children with diseases of the central nervous system, yet the mechanism of its production are not completely understood.

Glycosuria may be seen with severe infection or with the pancreatitis complicating mumps, and decreased sugar tolerance may also be seen in hyperthyroidism. Transient glycosuria may also occur in association with lesions of the pituitary or hypothalamus.

Claude Bernard's[1, 2] discovery that puncturing the floor of the fourth ventricle produced glycosuria in dogs encouraged many attempts to define, by experiments, a center in the brain concerned with carbohydrate metabolism.

Aschner[3] produced glycosuria by injuring the tuber cinereum in the floor of the third ventricle (Fig. 1). Brugsch, Dressel, and Lewy and Gassman[4] suggested the identification of a hypothalamic cell group with sugar metabolism when they found that piqûre into the dorsal nucleus of the tenth nerve, when followed by glycosuria, led to a retrograde degeneration in the periventricular nucleus, a cell group around the fornix bundle within the hypothalamus. Camus, Gournay, and Le Grand[5] produced glycosuria after tuberal lesions, and believed that the center for hyperglycemia lay in the tuberal and paraventricular nuclei[6, 7] (Fig. 1). Injury or puncture of the hypothalamic region or tuberal region with development of glycosuria has been recorded by a number of observers.[8-14]

Davis, Cleveland, and Ingram[15, 25] found that lesions in the ventromedial nucleus of the hypothalamus (Fig. 1) would ameliorate the symptoms of pancreatic diabetes and prevent the glycosuria and hyperglycemia produced by stimulation of the superior cervical ganglion. Brobeck and associates[16] were unable to confirm these findings, and stated that they were actually able to precipitate diabetes in susceptible animals in a few cases by placing lesions which caused hypothalamic hyperphagia and increased rate of food intake.

Houssay[17, 18] noted that a certain number of dogs had transient hyperglycemia after hypophysectomy, and that lesions of the nuclei of the wall of the third ventricle sometimes produced glycosuria in the rabbit. He was never able to produce a permanent hyperglycemia or glycosuria in dogs with either circumscribed or extensive lesions of the diencephalon.

Glycosuria and hyperglycemia have been produced by stimulation of the

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hypothalamus, by L'Hermitte[20] and others.[4, 21-23] Lewy and Gassman stated that they obtained hyperglycemia after stimulating the paraventricular nucleus of the hypothalamus. C. W. Harris[24] obtained a decrease in insulin sensitivity following electrical stimulation in the tuberal region.

There is no evidence from the experimental work that the control of blood sugar can be permanently altered by hypothalamic lesions. The experimental evidence that extirpation of the pituitary or hypothalamic damage produces an increased sensitivity to insulin and a lowered sensitivity to the hyperglycemic effect of adrenalin has led to the hypothesis of a hypothalamo-pituitary mechanism influencing carbohydrate metabolism. There is evidence that the hypothalamus influences the secretion of adrenalin as part of the general sympathetic

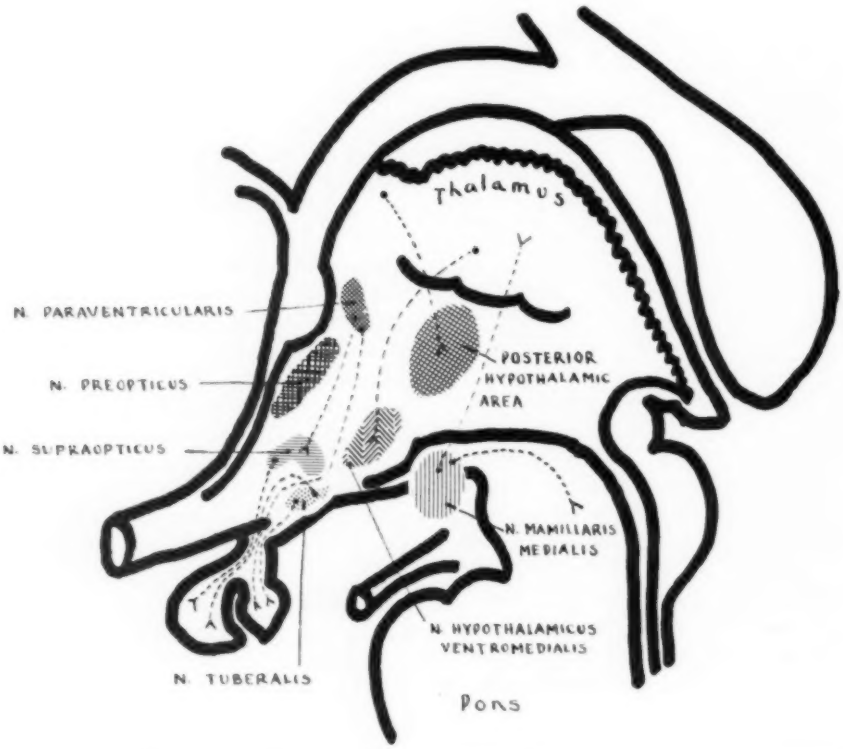


Fig. 1.—(Reproduced from Figure 2 on p. 281 of Endocrinology in Childhood by Dr. Lawson Wilkins, with his permission.)

Some authors[11, 13] reported hypoglycemia after injury to the anterior portion of the hypothalamus involving the chiasmal and tuberal regions. Negative findings after lesions in the hypothalamus have been recorded by Ranson and his colleagues.[27]

control[28, 29] by means of a pathway through the brain stem, spinal cord, and splanchnic nerves. Glycogenolysis may result, with alterations in the blood sugar that have to be separated from those alterations following pancreatectomy. In the latter case, the continuance of the hyperglycemia and glycosuria is independent of liver glycogen, while the former disappears when the glycogen stores are exhausted.

Information concerning the connections between the pituitary and hypothalamus and between the hypothalamus and brain stem is incomplete. Ranson showed that the most important tract functionally innervating the neurohypophysis was the supraopticohypophyseal tract to the posterior pituitary. Harris stimulated this tract but was unable to obtain an increase in the blood sugar. Electrical stimulation of the lateral wall of the third ventricle above the mammillary body will lead to all the signs of sympathetic activity.[30] Ranson believed that fibers travel down through the brain stem via the lateral part of the substance of the tegmentum, but most authorities hold they descend close to the floor of the fourth ventricle in a bundle termed the fasciculus longitudinalis dorsalis of Schutz. Confirmation of either theory, however, is lacking. Beattie and his associates[31] have found evidence of nerve tracts connecting the hypothalamus with spinal sympathetic centers, and have shown that lesions involving certain nuclei of the posterior part of the hypothalamus are followed by the degeneration into the spinal cord. However, this work has not been confirmed.

Injury to the tegmentum of the pons[29] will cause a temporary glycosuria and hyperglycemia in animals. Following transections at the level of the upper pons or through the midbrain, there is decreased tolerance to glucose, according to Anderson and Haymaker.[32]

In summarizing the experimental evidence, there appears to be a mechanism involving the diencephalon, whereby manipulation, stimulation, or injury can produce a temporary hyperglycemia when lesions are placed in the paraventricular, tuberal, or ventromesial nuclei of the hypothalamus: roughly within an area between the descending column of the fornix and the tractus mamillo-thalamicus. Injury and transection at the level of the midbrain or pons will also produce transient hyperglycemia.

CASE REPORT

J. C. W., a 4-year-old boy, was seen for the first time at his home, at 5:30 A.M. on Jan. 8, 1954. His parents had been awakened two hours previously by his vomiting. He had vomited about four times, and had alarmed his parents because he looked ill and appeared to be acting in an unusual manner. His extremities felt cold. When first examined he appeared acutely ill, had a gasping type of respiration, and presented an unusual appearance because of marked mottling of the skin of all extremities. He was delirious. He had never been sick before and his general health and development had been normal. He had acted normally at the time he was put to bed on the previous day. He had played in the yard and presented a normal appearance that day.

The child was taken immediately to the hospital. On admission his temperature was 104° F. He was delirious and his skin appeared very

pale. There was some cyanosis of the mucous membranes. His neck was stiff, and his pupils small, but equal, and reacted slowly to light. He made frequent irregular groping movements with the left hand. There was no paralysis or rigidity, and the deep-tendon reflexes were all equal but hyperactive. Babinski's sign was absent bilaterally. The child appeared well nourished and developed. The family history revealed that a paternal grandmother had diabetes.

A lumbar puncture was performed and grossly bloody fluid obtained. This finding was hard to evaluate as the child struggled during the procedure. A catheterized urine specimen showed a 4 plus sugar, no acetone, and normal sediment. Temperature at 8:00 A.M. was 105.6° F. It was felt impossible at this time to exclude the possibility that this was a case of diabetes mellitus and, because of the glycosuria and hyperglycemia, 50 u. of regular insulin was given. The patient also received intravenous drip of normal saline. By 9:30 A.M., the blood sugar was 139 mg. per cent. Temperature was 104° F. Pulse was 100, respiration 50, and blood pressure 120/70. The pupils were dilated. Convulsive twitchings were observed if any kind of stimulation was applied to the extremities. The patient was sponged with alcohol and cold water and given aspirin. By 10:30 A.M., urinalysis showed 2 plus sugar but no acetone.

Glucose was given intravenously for the first time shortly after this. The child became gradually comatose and developed respiration of the Cheyne-Stokes type. The pupils were constricted and the Babinski sign was present bilaterally. The urine contained a trace of sugar at 11:30 A.M. and the blood sugar fell to 78 mg. per cent. The pupils dilated, and the temperature was 105.3° F.

As there had been little clinical response after the insulin was given, the diagnosis of diabetes seemed doubtful, therefore, 30 c.c. of 50 per cent glucose was given intravenously without response. The possibility of this being encephalitis or intracranial hemorrhage was then considered. Respirations became shallow and finally ceased at 1:05 P.M. Artificial respiration with a closed circuit anesthesia machine was started, and the patient was transferred to another hospital and placed in a respirator. The lumbar puncture was repeated shortly before transfer and showed grossly bloody fluid.

On admission to the second hospital, at 3:00 P.M. on that same day, the patient's condition remained the same. He was comatose, with flaccid extremities, and widely dilated pupils that did not respond to light. Temperature was 95° F. Blood pressure was 70/0. Color appeared good after he was placed in a respirator. Blood sugar at 4 o'clock was 24 mg. per cent. Because of this, 5 Gm. glucose was given in 20 c.c. doses intravenously. At 6:30 P.M. the blood sugar had risen to 214 mg. per cent. Epinephrine and later Levophed were given because of the hypotension with some response. Urinalysis at 7:30 P.M. showed 1 plus sugar. By midnight, the blood pressure was being maintained well on the Levophed.

By 8 o'clock the next morning, the patient appeared little improved. Vital signs were stable and he was moving all his extremities spontaneously and in response to stimulation. Pupils were widely dialated and irregular. Babinski's sign was present bilaterally. By 11:00 A.M. of that day, the blood pressure had dropped to below 60 and Levophed was started again. Lumbar puncture was repeated and showed deep-pink colored fluid. At 7:40 P.M. the blood pressure dropped suddenly and was followed rapidly by cardiac arrest, and death.

Autopsy Findings.—No gross or microscopic abnormality was noted in any of the visceral organs other than acute confluent bilateral bronchopneumonia. The liver, adrenals, and pancreas appeared normal. The pituitary was intact.

The brain weighed 1,250 grams and appeared swollen and pale with flattening of the cerebral gyri. Recent subarachnoid hemorrhage covered the cervical cord, brain stem, and region of the fourth ventricle. A diffuse area of neoplastic tissue involved the base of the brain extending anteriorly from the superior pole of the pons and surrounding the optic chiasma and stalk of the pituitary gland, principally on the right side. The tumor tissue was translucent, grayish-red, soft, and flat. The major branches of the circle of Willis were thin-walled and patent. A midline sagittal section revealed recent massive hemorrhage into the ventricular system with disruption, distortion, and compression of the thalami (Fig. 2). The region of the hypothalamus, optic tract, and mammillary bodies on the right side appeared grossly to be infiltrated and replaced by a neoplasm. A coronal section through the midportion of the left half of the brain revealed hemorrhage and softening of the thalamus, and blood clots in the lateral ventricle.

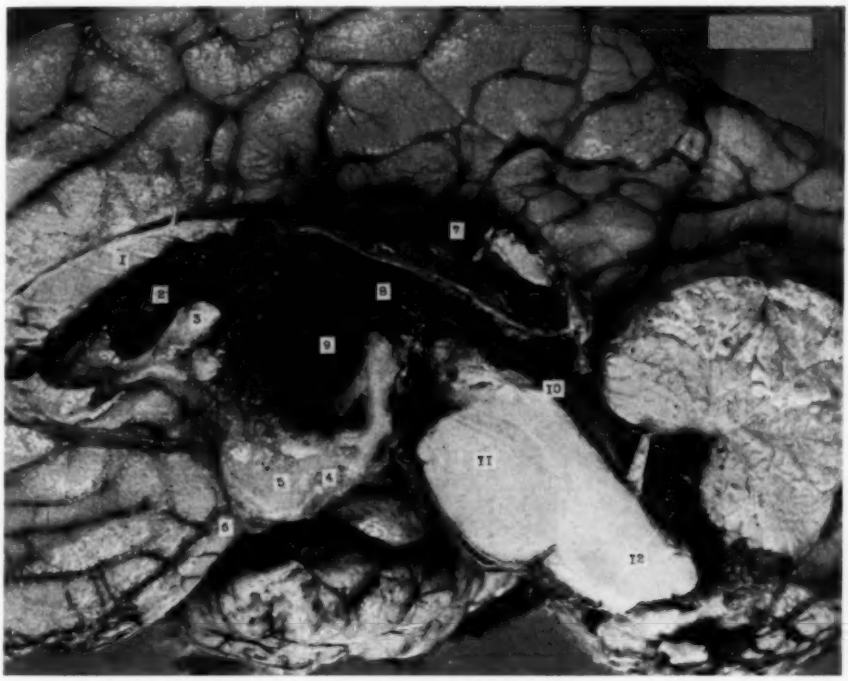


Fig. 2.—Right sagittal section of the brain showing the hypothalamic area. *1*, corpus callosum; *2*, lateral ventricle; *3*, septum pellucidum; *4*, mammillary body; *5*, hypothalamus; *6*, optic chiasma; *7*, choroid plexus; *8*, third ventricle; *9*, region of thalamus; *10*, fourth ventricle; *11*, pons; *12*, medulla.

Study of the brain after fixation confirmed the above findings and revealed, in addition, that the tumor infiltrated the subthalamic region on the right side for a distance of more than 1 cm. and was continuous with the choroid plexus of the fourth ventricle. The entire area of tumor infiltration and hemorrhagic destruction of brain substance was circumscribed anteriorly by the stalk of the

pituitary and the septum pellucidum, and posteriorly by the anterior superior pole of the pons. Both the right and left thalami and hypothalami were involved, but the major alterations were chiefly in the right side of the mid-sagittal plane. The tissues adjacent to the left wall of the third ventricle showed hemorrhage and softening for a distance of several millimeters.

Multiple histologic preparations revealed diffuse and focal hemorrhages in the thalami (Fig. 4), and hypothalami with associated edema, vacuolization, and glial reaction. The tumor consisted of small oval cells with basophilic nuclei and scant cytoplasm in a loose fibrillar stroma without organization or rosette formation (Fig. 3). Tumor cells surrounded and infiltrated the stalk of the pituitary, optic chiasma, optic tract, thalamus, and hypothalamus on the right side and floor of the third ventricle. The tumor was considered to be a locally invasive ependymoma.

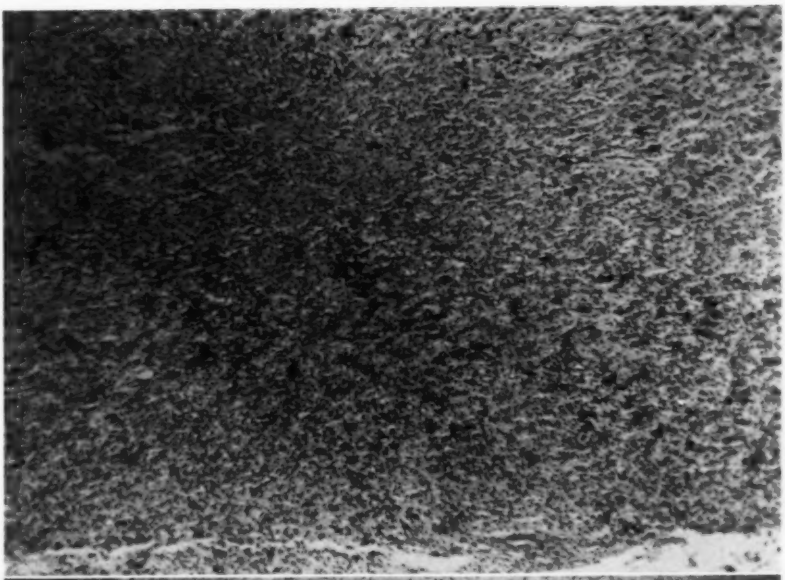
Outside of these findings, no significant pathologic alterations were encountered elsewhere in the body.

COMMENT

This case presented several interesting features that are worthy of comment. The initial hyperglycemia was followed by hypoglycemia similar to the findings of Barris and Ingram[13] in some of their dogs where the anterior hypothalamus had been damaged. The patient's hydration appeared normal, a finding Dorothy Russell[34] noticed in her case, and which is unusual in diabetes mellitus. Acetone was never present in the urine in this case, although Russell says it may occur to a limited degree, and ketonuria was present in some of the cases mentioned later. The finding of acetone in the urine is evidently of no value in differentiating the hyperglycemia of central origin from that due to pancreatic diabetes. Levophed and epinephrine both tend to raise the blood sugar so that the blood sugar values after these drugs and glucose were given are probably inaccurate. The initial values, however, are significant as the child had had nothing by mouth for at least eight hours prior to the first urine and blood sugar estimations.

Russell believed that in her case there was a sympathetic hyperglycemia due to irritation from the tumor in the hypothalamic region, and some similar mechanism was probably the cause of the hyperglycemia in this case. Beattie[35] felt that marked stimulation of the sympathetic portion of the hypothalamus could explain the intense vasoconstriction of the skin vessels (to eventual mottling), increased body temperature and sweating of the sympathetic type (not accompanied by vasodilation) in this case. He also thought it extremely unlikely that any persistent hyperglycemia could be explained on the basis of intense sympathetic stimulation. The failure of respiration together with rise in body temperature suggested, he thought, that either the thermosensitive zone of the hypothalamus had been destroyed, or the pathways from it had been interrupted, in this case.[35] The alternative explanation was that a marked rise in intracranial pressure could have caused respiratory failure. It is also possible that distention of the ventricles with blood could have contributed to the hyperglycemia, as hyperglycemia has been reported even after pneumoencephalography,[36] supposedly due to ventricular distention.

Fig. 3.



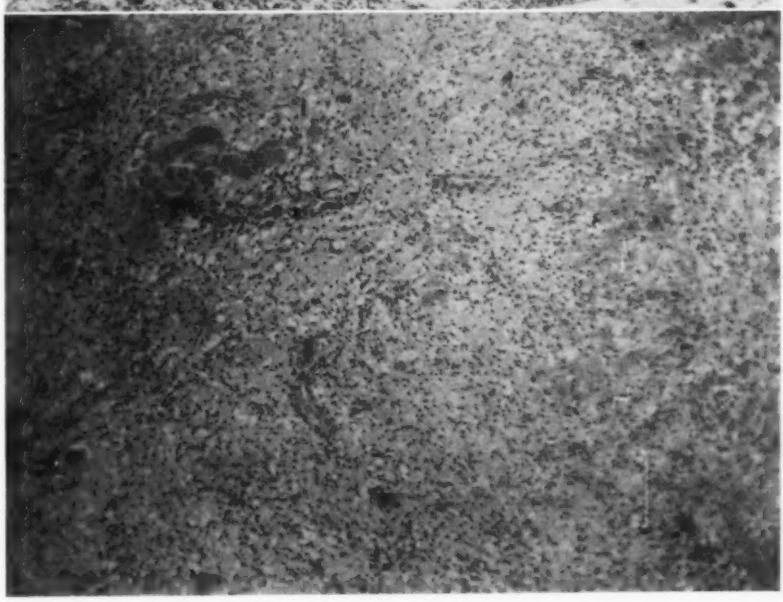


Fig. 4.

Fig. 3.—Tumor in the wall of the third ventricle.
Fig. 4.—Hemorrhage and degeneration in the region of the hypothalamus.

TABLE I. CLINICAL REPORTS OF BRAIN DAMAGE ASSOCIATED WITH DISTURBANCES OF CARBOHYDRATE METABOLISM

CASE	HISTORY	TREATMENT	OUTCOME	AUTOPSY FINDINGS
Case 1[34]	Diabetes of 5-year duration	Insulin with little response; restricted carbohydrate diet	Death	Internal hydrocephalus. Cyst from the anterior pillars and body of the fornix, behind the foramen of Monro, projecting into the third and left lateral ventricle. Tuberculosis of the trachea, aorta and, also, the right adrenal and left lung
Case 2[34]	Unresponsive diabetes	Insulin	Death	Tumor of the third ventricle
Case 3[34]	Diabetes of 5-year duration	Insulin of little use	Death	Cyst of the midbrain. Degeneration of the pancreas
Case 4[45]	Glycosuria following a head injury; diagnosis cerebral hemorrhage	None	Death	Subarachnoid hemorrhage, implicating all structures of the base of the brain, including the tuber cinereum. Pituitary normal
Case 5[45]	Hypertension. Patient developed coma and glycosuria	None	Death	Extensive hemorrhage into the pons, extending upward into the interpeduncular space, and compressing the third ventricle. (?) hypothalamic pressure (?) interruption of descending pathways from this area in the tegmentum of the pons
Case 6[45]	Patient with glycosuria following a stroke	None	Death	Hemorrhage in the left half of the midbrain, thrusting portions of the midbrain upward to compress the cavity of the third ventricle. Portions of the tegmentum of the midbrain and pons were destroyed by hemorrhage
Case 7[45]	Mental confusion and aphasia, incontinence, weakness of the legs, and mild diabetes	Insulin	Gradually the glycosuria increased and the patient developed psychotic manifestations and died	Cyst of the pulvinar of the left thalamus, extending mesially and posteriorly to overlap and occlude the aqueduct of Sylvius, causing internal hydrocephalus, and marked dilatation of the third ventricle. Microscopically, there was cell loss and retrograde changes in the nucleus paraventricularis and in the substantia grisea of the hypothalamus
Case 8[45]	Alcoholism and duodenal ulcer, with a disturbed mental state. Blood sugar on the day of death was 299 mg. per cent	None	Death	Large duodenal ulcer. Multiple hemorrhages in the anterior and superior aspects of the hypothalamus, implicating the superior portion of the nucleus paraventricularis. The nucleus supraopticus showed hemorrhage on both sides. There was destruction of many cells in the nucleus paraventricularis, and cell loss in the substantia grisea of the third ventricle and the nucleus tuberalis lateralis

Case 9[55]	Patient with diabetes of 2-month duration; urinalysis showed a 4 plus reaction for sugar and fasting blood sugar 240 mg. per cent	Hyperglycemia did not respond well to insulin therapy. Blood sugar at time of death 325 mg. per cent	Progressive downhill course and death	Cyst in the mid-portion of the medial nucleus of the thalamus on the left side, and extending posteriorly to the posterior border of the left superior colliculus. It extended laterally to the internal medullary lamina and medially to the wall of the third ventricle. Pressure from the cyst resulted in hydrocephalus of the third and lateral ventricles by obstruction of the aqueduct of Sylvius. Pancreas was normal
Case 10[56]	Patient with diabetes of 5-year duration	Insulin, but followed no definite plan and the diabetes was poorly controlled	Death	Massive infarction of the entire anterior lobe of the pituitary. Excessive glial proliferation throughout the hypothalamus, especially intense in the paraventricular nucleus and the nucleus supraopticus. There was also toxic nephrosis and tuberculosis of both lungs and acute ileitis
Case 11[59]	Patient had diabetes following two severe falls with a loss of consciousness	Insulin with poor response	Death	Meninges were thickened at the base of the infundibulum, with an area of about 2 mm. across where the meninges were thickened from irregular collagen fibrils. There were round cells in this area. Vessels were large and congested and showed fibrous thickening and edema. There was an area of gliosis reaching from the tuberal region to the bottom of the third ventricle. This area contained few vessels. There were several degenerative changes in the ganglion cells of the tuber cinereum, and the ependymal mucosa of the third ventricle showed focal ependymitis granularis. Substance of the hypothalamus on both sides of the third ventricle was edematous. Vessels were congested and there was perivascular hemorrhage. There were hemorrhages in both paraventricular nuclei, and some degenerative changes in these nuclei and in the cells of the nucleus mammillo-infundibularis. Pancreas showed hydropic degeneration. There were few islets, there was an increase in the alpha cells. There was glycogen in the liver and in the epithelium of Henle's loop in the kidneys

TABLE I—CONT'D

CASE	HISTORY	TREATMENT	OUTCOME	AUTOPSY FINDINGS
Case 12[37]	Case of diabetes with neurologic symptoms	Diet and insulin. Neurological symptoms became progressively worse. Patient developed a hemiparesis	Coma and death	Large glioblastoma in the left temporal region spreading down into the hypothalamus, but not involving the pituitary. Pancreas showed degenerative changes compatible with diabetes mellitus
Case 13[35]	Patient with persistent hyperglycemia of over 5-years' duration	Not known	Death	All the more medial nuclei of the hypothalamus, lying near the floor of the third ventricle, were destroyed from the preoptic area to the anterior edge of the mammillary bodies. There was a cyst filling the sella turcica, but the pituitary gland was not wholly destroyed. There was no evidence of Simmonds' syndrome
Case 14[63]	Patient with symptoms of increased intracranial pressure, who had previously been treated for diabetes; blood sugar at the time of admission was 160; urinalysis was negative	Operation carried out in two stages; a large meningioma situated at the foramen magnum, with its anterior surface resting on the medulla, was removed	Postoperatively, there was evidence of medullary disturbance as shown by glycosuria and blood sugar varying from 72 to 273 mg. per cent. From the tenth day postoperatively, the patient showed no signs of diabetes or glycosuria	

DISCUSSION

Clinically it has been known for a long time that cerebrovascular accidents,[37] trauma, meningitis, and tumors, may cause hyperglycemia and glycosuria. But that this is of any significance has been challenged by some authorities.

Cushing stated he had never seen even transient glycosuria after operations in the hypothalamic area. Joslin and associates[39] have expressed the opinion that there is no justification for assuming a cerebral role in the etiology of diabetes mellitus, and that where the two are associated there is coincidental hereditary weakness of the pancreas. One interesting observation that was made by Cushing is worth mentioning, and that is the high incidence of acromegalics who developed diabetes. In a series of 100 cases of acromegaly, Davidoff[40] and Cushing found that 25 per cent had glycosuria and 12 per cent had diabetes mellitus.

There have been few reports of abnormalities in the hypothalamus in diabetes mellitus. Dresel and Lewy[41] reported studying the brains of four diabetics and found changes in the globus pallidus in all these cases. Experimenting in dogs, Urechia and Nitescu[42] reported degeneration in the paraventricular nucleus of the hypothalamus in four animals after pancreatectomy. Nicolesco and Raileanu[43] reported pathologic changes in the brains of two diabetics, and there is an account in the French literature of a man with central nervous system syphilis and diabetes who showed changes in the periventricular nucleus at autopsy.[44]

In the recent American literature, Vonderahe[45, 46] has studied the hypothalamus carefully in a number of diabetics and, in an account of 15 patients, reported a loss of cells in the paraventricular nucleus ranging from 3 to 65 per cent. In many of these, there was also cell loss in other neighboring areas.

These findings have not been confirmed by others. Warren and LeCompte[47] state they have not found any abnormality in the central nervous system in their cases, and mention a large number of cases studied by Hicks in which the findings were similar to theirs. This appears to be the generally accepted view at the present time: that in uncomplicated diabetes mellitus, there are no abnormalities in the hypothalamus at autopsy.

A review of the literature revealed a number of cases where there appeared to be an association between a disturbance of carbohydrate metabolism and a lesion in the brain confirmed by autopsy (Table I). The patients in cases 1, 2, and 3 had definite cerebral lesions: In 2 cases, in the hypothalamus and in the other, in the midbrain. Cases 4 to 8 were reported in detail by Vonderahe and are interesting because in 3 the urine was examined before the illness began and no abnormality was found. Patients 9 and 10, also described by Vonderahe and his associates, both had definite hypothalamic damage at autopsy. Case 10 was an example of the Houssay phenomenon. Patient 11 had hyperglycemia and glycosuria following head injury. Although there is little evidence to support the concept that trauma may lead to diabetes mellitus,[60-62] it seems difficult

to explain the association of hypothalamic damage and glycosuria as coincidental in case 11. Autopsy showed extensive damage in the hypothalamic region. The patients in cases 12 and 13[35, 37] both had diabetes and hypothalamic damage. The patient in case 14 was cured when a meningioma that rested on the medulla was removed.

The most significant finding from a review of the clinical cases seems to be the long duration of the diabetes in the patients in cases 1, 3, 9, 10, 12, and 13, associated with definite autopsy findings of hypothalamic damage. It seems difficult to explain all these findings either as coincidence or on the basis of a sympathetic stimulation which is usually transient.

CONCLUSION

There is some clinical evidence to support the experimental work showing that transient hyperglycemia and glycosuria can be produced by lesions or stimulation of the hypothalamic region. A case is reported in a child where a hypothalamic tumor was associated with a disturbance of carbohydrate metabolism. Several cases are reported in the literature of diabetes of several years' duration associated with hypothalamic damage, and the association may not be coincidental. A more detailed examination of the brain and hypothalamus in every case of diabetes with cerebral symptoms might be valuable in shedding more light on this difficult problem.

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Of Cause and Effect

". . . the instinctive act of sucking under circumstances unfavorable to the infant obtaining the food for which its system craves, is a fruitful source of disease to infants and puerperal women. As regarded infants, the exercise of fruitless and consequently prolonged and forcible suckings is attended by an excessive reflex secretion of gastric juice, which acts upon the mucous coat of the intestinal canal, causing various degrees of injury thereto. The frequent loose and green stools of infants are the evidence of this process being in operation. . . . The index to the health of the mother and child is the state of the child's bowels; if frequent and loose, one or other is, or will be ill; if only one or two stools a day, both are pretty sure to be well and thriving."

From a lecture by Thomas Ballard on "A New Theory of the Cause of Some of the Diseases of Infants and the Puerperal State" before the Harveian Society of London, reported in the BRITISH MEDICAL JOURNAL, January 29, 1859.

THE ACQUISITION OF FECAL FLORA BY INFANTS FROM THEIR MOTHERS DURING BIRTH

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THIS paper is a report on the frequency with which a newborn infant derives its initial fecal flora from his mother. The sources of such initial fecal flora in a newly born infant have as yet not been established. That it is obtained after birth is a well-known fact. In treating of this matter, certain postulates have been made. Thus, it has been postulated that the infant's mother, the nursery personnel, or the environment may be contributing factors. The investigation reported here has resulted in one interesting fact which may prove helpful in the final determination of the subject under review, viz., that in 25 per cent of the cases studied, the infant's mother proved to be the source of the initial fecal flora. Another interesting fact discovered in the course of the investigation indicated that the majority of the infants found to to have organisms of the Klebsiella-Cloacae group most probably obtained them from their environment.

The Grady Memorial Hospital in Atlanta, Georgia, at the time in which this study was conducted, housed its obstetrical patients in two separate buildings. One unit of delivery rooms and full-term nurseries was in a new building with modern facilities, and a second unit was in the old main hospital building. The same medical staff cares for patients in both, but there are separate nursing staffs. The major difference between the two groups, therefore, is in the environment rather than in the care given to the patients.

The obstetrical service of Grady Memorial Hospital averages over 6,000 deliveries a year. Twenty per cent of all deliveries occur in the old building, group A, where the usual stay for mothers and their infants is 5 days. Mothers and infants in the new building, group B, are usually discharged 24 hours after delivery, but for this study the time was extended to 3 days.

In this hospital, the newborn infant is shown to his mother shortly after delivery, in the delivery room if possible, but she is not allowed to handle him at that time. Her first contact with the baby is eight hours after his birth when feeding is begun. Thereafter, breast-fed babies are brought to their mothers at four-hour intervals, bottle-fed babies twice daily, at 10:00 A.M. and 6:00 P.M.

During March and April, 1956, while this study was being conducted,

From the Communicable Disease Center, Public Health Service United States Department of Health, Education, and Welfare; and Grady Memorial Hospital, Atlanta, Ga.

there were 1,024 deliveries, 889 of them full-term births. Twenty parturient mothers (13 in group A and 7 in group B) were studied by culture methods during a period of 6 weeks. All of the babies were full-term, single births, and three of them were breast-fed.

Upon admission, parturient women were told of this study, and consent of those who wished to participate was obtained. A medical-obstetrical history was taken, which included information suggestive of enteric illness, either in herself or in any member of her household within the past twelve months. All members of this study group gave no information suggestive of enteric illness during this period.

METHOD

Rectal swab specimens were obtained from the mother before delivery (both before and after enema when possible), but none after delivery. Throat and rectal swab specimens from the newborn infant were taken immediately after birth in all but two instances while the infant was still on the sterile field, and additional rectal swab specimens were taken at 24, 48, and 72 hours after birth.

The specimens were plated directly onto MacConkey's and Salmonella-Shigella (SS) agar plates, and inoculated into brilliant green tetrathionate broths. After 18 hours' incubation, the broths were streaked onto brilliant green agar plates. All plates were screened for Shigella and Salmonella by standard methods.[1] Twenty coliform colonies were picked (when present) from each of the MacConkey agar plates. Ten *Escherichia coli* were confirmed biochemically and typed serologically. Where no correlation was found between the flora of the mother and her infant, the remaining ten colonies were examined.

Cultures of organisms of the Klebsiella-Cloacae group were biochemically confirmed. If the same biotype was recovered from both mother and infant, the organisms were identified serologically.

LABORATORY RESULTS

On the basis of somatic antigen, the *E. coli* species may be divided into more than 140 distinct serotypes. From the 20 mothers studied, 22 *E. coli* serotypes were isolated, and from the 20 infants studied, 11 *E. coli* serotypes were isolated. Seven types identified from the mothers were found to be present in the infants.

The instances in which there was correlation between the mother's and the infant's fecal flora are presented in Table I. The laboratory data presented in this table show that five of the infants excreted the same *E. coli* biotypes and serotypes as their mothers. One infant, Case 4, had the same *E. coli* biotype as the mother; however, the organism failed to react in the known *E. coli* antiserums. Serotypes excreted by the mother were found in the throats of two of the infants at the time of delivery, Cases 1 and 6. One infant, Case 2, had the same serotype as her mother at 24 hours, and two infants, Cases 3 and 5, excreted the same serotypes as their mothers at 48 hours.

An enteropathogenic strain, *E. coli* 055B5, was found in both the mother and infant not associated with illness (Case 3). It is probable that the

initial rectal swab culture obtained on Case 1 resulted from skin contamination of the prianal region and was not derived from the meconium itself. Olsen[2] states that it is highly probable that older authors are right when they believe that the intestinal canal is sterile at the time of birth.

TABLE I. INSTANCES OF CORRELATION BETWEEN THE TYPE SPECIFIC E. COLI IN THE FECAL FLORA OF THE MOTHER AND HER NEWBORN INFANT

CASE NO.	NURSERY GROUP	MOTHER'S ADMISSION RECTAL SWABS		BABY'S DELIVERY SWABS		BABY'S RECTAL SWABS (HOURS POSTDELIVERY)		
		PRE-ENEMA	POST-ENEMA	RECTAL	THROAT	24	48	72
1	B	0:11 AD01	NS	0:11 AD01	0:11 AD01	0:11 AD01	0:11 AD01	0:11 AD01
2	B	AD01	NS	NG	NG	AD01	NS	NS
3	B	0:55B5 0:4	0:55B5 0:4	NG	NG	0:83	0:55B5 0:4 0:83	NS
4	A	NR	NR	NG	NR 0:81	0:X1R	0:X1R	NR
5	A	0:62 0:77	NS	NG	NG	0	0:62	0:62
6	A	0:9 0:92R	0:9 0:135	NG	0:9 0:135	0	0:9 0:135	0:9

NS = No specimen.
NG = No growth.
NR = *E. coli* does not react serologically in the known *E. coli* antiserums.
R following a *E. coli* type = this organism is related to this *E. coli* type.
AD01 = Alkalescens Dispar 01.
0 = *E. coli* not present.

TABLE II. INSTANCES WITH NO CORRELATION IN THE FECAL FLORA OF THE MOTHER AND NEWBORN INFANT

CASE NO.	NURSERY GROUP	MOTHER'S ADMISSION RECTAL SWABS		BABY'S DELIVERY SWABS		BABY'S RECTAL SWABS (HOURS POSTDELIVERY)		
		PRE-ENEMA	POST-ENEMA	RECTAL	THROAT	24	48	72
1	A	0:1	0:1	NG	NG	0	0	0
2	A	0:11	NS	NG	NG	0:X1R	0:X1R	0:X1R
3	A	NR	NR	NG	NG	0	0	0
4	A	NS	0:62 0:1	NG	NG	0	0	0
5	A	0:21	0:21	NG	NG	0	0	0
6	A	NS	0:2	NG	NG	0	0	0
7	A	0:20 0:88 0:127R NR	 NR 0:76R	NG	0	0	0:X1R	0:X1R NR
8	A	0:6	0:6	NG	NG	0	0	0
9	A	NS	0:73 0:61 0:25 NR	NG	NG	0	0	0
10	B	0:19a 0:82	NS	NG	NG	NG	NG	NG
11	B	0	NS	NG	NG	NG	NG	0:X2
12	B	0:48	0:48 0:7	NG	NG	NG	0:6	NR
13	B	NS	0:99	NG	NG	NG	NS	NS

The key to this table is the same as that given in the footnotes for Table I.

The instances in which the *E. coli* types isolated showed no correlation between mother and newborn infant are summarized in Table II. Each of the 13 mothers carried *E. coli* in their stools, but in 9 infants no coliform organisms were isolated. In 4, types not found in their mothers appeared.

Cultures containing organisms of the Klebsiella-Cloacae group can be found in Table III. Cultures containing organisms of the Klebsiella-Cloacae group were biochemically confirmed. In Case 13 a possible biochemical relationship existed between the organisms of the mother and her infant. The infant in Case 17 had two Klebsiella-Cloacae biotypes, one of which could possibly have been the mother's; the other one could not have been the same. Serological typing of these organisms in Case 17 showed the serotypes to be dissimilar.

One mother was carrying a Shigella at the time of parturition but the infant did not become infected (Case 19).

TABLE III. KLEBSIELLA-CLOACAE GROUP OF ORGANISMS

CASE NO.	NURSERY GROUP	MOTHER'S ADMISSION RECTAL SWABS		BABY'S DELIVERY SWABS		BABY'S RECTAL SWABS (HOURS POSTDELIVERY)		
		PRE-ENEMA	POST-ENEMA	RECTAL	THROAT	24	48	72
a	A	0	0	NG	NG	+	+	+
b	A	0	NS	NG	NG	+	+	+
c	A	+	+	NG	NG	+	+	+
d	A	0	0	NG	NG	+	+	+
e	A	NS	0	NG	NG	+	+	+
f	A	+	+	NG	NG	+	+	#9
g	A	+	0	NG	0	+	+	+
h	A	+	NS	NG	NG	+	+	+
i	A	NS	+	NG	NG	+	+	+
j	A	#10	+	NG	+	#17	+	+
k	A	0	+	NG	0	+	0	+
l	A	0	+	NG	NG	+	+	+
m	A	NS	0	NG	NG	+	+	+
n	B	0	NS	0	0	0	0	0
o	B	0	NS	NG	NG	NG	NG	NG
p	B	+	NS	NG	NG	NG	NG	0
q	B	+	NS	NG	NG	+	NS	NS
r	B	0	0	NG	NG	NG	0	+
s	B	NS	+	NG	NG	NG	NG	NG
t	B	0	0	NG	NG	+	+	NS

0 = Klebsiella not found.
NS = No specimen.
NG = No growth.
+ = Klebsiella found.
Nos. 10, 17, and 9 = Types found.

DISCUSSION

The results we obtained indicate that the mother is a frequent source for her infant's initial fecal flora. Twenty-five per cent of the infants observed exhibited *Escherichia coli* which belonged to the same O groups as those found in the mother. In addition, these organisms were found to be present in the throats of two of the infants at the time of delivery. With the possible exception of the mother and the infant that exhibited *E. coli* which did not belong to any of the known O serological groups, the source from which the

other infants in the study derived their initial fecal flora could not be ascertained. Another 8 infants had only organisms of the Klebsiella-Cloacae group, and 2 failed to show growth of any enteric organisms during the period of observation. It is reasonable to postulate that the 6 infants displaying strains of *E. coli* different from the maternal strains had received them from other human sources within the nursery. This is not necessarily true for the Klebsiella-Cloacae group of organisms which exist widely in nature, in soil and in dust, independent of a fecal source. The differences between the nursery environments for the infants in groups A and B have been mentioned earlier. In comparing the results for the 24-, 48-, and 72-hour specimens, organisms of the Klebsiella-Cloacae group were found in 38 of 39 cultures obtained from the infants in nursery A, but in only 4 of 16 cultures obtained from the infants in nursery B. Organisms from this group were found in all 13 of the "A" infants, but in only 3 of the 7 "B" infants.

Organisms of the Klebsiella-Cloacae group were isolated from specimens collected from 8 of the 13 mothers in unit A and 3 of the 7 mothers in unit B; hence, 11 of the 21 specimens from the former, and 3 of the 9 specimens from the latter, were positive.

In Case 3 (Table I) *E. coli* 055B5, one of the enteropathogens, was found in the mother and in the infant at 48 hours. The infant had been isolated from birth for other reasons and had no contact with his mother until discharge. He remained asymptomatic during the period of observation. Ocklitz and Schmidt,[3] in their study, have reported one case in which the same enteropathogenic *E. coli* serotype was found in the mother's stool on the last day before her admission to the antenatal clinic and, after delivery, in the rectal swab of her newborn infant. Another mother was carrying a Shigella at the time of delivery but the infant did not become infected; isolation was carried out as a precautionary measure. The discovery that two mothers were harboring known pathogens at the time of delivery further emphasizes the need for constant vigilance to prevent the spread of enteric organisms in nurseries for newborn infants.

SUMMARY

1. Twenty mothers and their infants were studied to determine to what extent infants derived their initial fecal flora from their mothers.

2. Laboratory results showed that five of the infants exhibited the same *Escherichia coli* serotypes as those found in their mothers. One infant had an *E. coli* biotype identical to that in her mother, but the organism did not react in the typing serums now available. The study showed that 25 per cent of the infants had the same fecal flora as their mothers.

3. Two of the twenty mothers were harboring known pathogens at the time of delivery. An enteropathogenic *E. coli* present in one was isolated from her infant at 48 hours. The Shigella identified in cultures from the other was not isolated from the infant during the period of observation.

4. The presence of organisms of the Klebsiella-Cloacae group in only 4 of the 18 specimens obtained from the infants housed in the new, modern unit, and in 38 of the 39 specimens obtained from the infants cared for in the older building with less adequate facilities, suggests the environment as an important source of these bacteria.

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Even as Now

In an issue which reported 111 cases of diphtheria and scarlatina in the week ending January 22, 1859, in London, the *British Medical Journal* of January 29, 1859, used an article which stated:

"It is to be feared that diphtheria, like charity, is made to cover a multitude of sins, and cloke diseases to which it has no resemblance. Let us be careful, whilst we seek to suppress quackery, we do not permit any fashionable title to be used, on *medical authority* at least, which the pretender might turn as a weapon against us, with the rebuke 'tu quoque'."

THE PARENTS OF RETARDED CHILDREN SPEAK FOR THEMSELVES

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WITHIN the last decade there has been vast development and rapid progress in the total area of mental retardation—more and better resources; specialized clinical and counseling services; training, educational, and recreational facilities; medical research; and financial aid. Concomitantly, there has been widespread interest in professional circles as well as in the community, increased understanding, acceptance, and tolerance of the mentally retarded child and his family. Much of the credit for the impetus to this important movement belongs to the parents of retarded children who, because of their persistence, perserverance, and courage, have shown the way. It is the parents themselves who have given us clues about their own capacity and strength to find the solutions and resolutions to their problems.

Although much has been accomplished, one area that is a constant source of difficulty is that of communication between parents and professional personnel. Frequently the parents of a retarded child go away from a contact with a physician, psychologist, or social worker with a good deal of justifiable dissatisfaction. This is not an isolated occurrence but tends to be rather widespread and, as professional persons, we must assume the responsibility and blame for these difficulties. The services that are offered can and should be improved. As a means of improving these services, the author enlisted the participation of the Maryland Society for Mentally Retarded Children and interviewed the parents in the following exploratory study.

With the approval of the officers and members of the Society, a letter was sent to every fourth member stating the purpose of the study. A questionnaire was developed as a general guide, with the full knowledge that this study would produce qualitative material of importance although not statistically impressive. In general, the guide fell into the following categories: (1) identifying data, (2) when retardation was first suspected by parents, (3) consultations by specialists, (4) counseling by professional persons and parents' reactions to counseling, and (5) value of group organization to the parents. Interviews were held by the author in the Harriet Lane Psychiatric Clinic; the average length of interview time was approximately 1 hour and, with few exceptions, it was the mother who came for the interview. Of a group of 50 to whom letters were sent and follow-up contacts made, 40 were seen; of the 10 remaining, the majority could not be

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reached and only 3 refused to participate. It should be noted that the group was a highly selected one, and the material is based on recall; therefore, the study does not lend itself to usual statistical methods.

In general, the parents can be described as an intelligent group of young and middle-aged people, with small families of 2 and 3 children, of the white race, and the middle socioeconomic class. Diagnostically, the children could be placed into the following categories: 19 mongoloid, 15 brain damaged, 1 epileptic, 1 seriously emotionally disturbed, and 4 of unexplained etiology. There was 1 instance of a family with two retarded children.

Answers to the factual questions of "When did you first suspect something was wrong?" "Was someone professionally consulted at that time?" and "Who really told you your child was retarded?" produced difficulty in pinpointing answers. One explanation is the time lapse and the problem of recall, since this material was gathered from several months to many years after the patient was diagnosed as retarded. However, other factors that bear consideration are (1) problems in diagnosing, and (2) the parents' reactions to the seriousness of the problem of retardation, to their feeling of difference from other parents, and the resultant feelings of fear and anxiety.

Often there is much uncertainty around diagnosis because many different factors must be weighed and evaluated such as (1) physical, (2) emotional, and (3) limitations in the tests themselves and the difficulties surrounding the testing, particularly of young children. The process of considering physical factors that complicate accurate evaluation frequently involves referral to many different specialists with their variety of opinions and, certainly, their uniquely different ways of handling the parents. It was not unusual to hear such expressions as: "My doctor did not know whether his slowness was due to his mental condition or to his physical sickness." "The doctor was confused as to whether the child could hear." "The doctor's first impression was muscular dystrophy and then in another examination he thought he was just retarded." Occasionally the influence of emotional factors must be considered, which necessitates intensive involvement of the parents in recapitulation of bitter life experiences. The limitations of the tests themselves, just in terms of evaluating intelligence, lend another element of doubt. Certainly the innumerable difficulties in having the child perform at his best and obtaining as much as possible from him create questions and doubts. In other words, are the test results representative of the child's intelligence? And, lastly, the adequacy and skill of the tester add another problem to the welter of confusion.

Mention of retardation creates a serious impact on parents, which is understandable in view of the attitude of society and the problems of the intellectually limited child achieving a safe, secure place in our culture. The very practical aspects of everyday living, training, schooling, recreation and, lastly, occupation and self-support have been almost insurmountable. It is no wonder then that usual responses were: "It's like someone came to you and told you your

child was dead." "When we were told, it was a terrible shock—you stop living." "I was on the verge of a nervous breakdown." It was not surprising, therefore, that these reactions were followed by acute feelings of "aloneness," "difference," being set apart from the rest of the world, rejection, and lack of interest in the children and their problems. This is vividly illustrated by such comments as: "None of the doctors said anything to me; I couldn't even get any schooling for him." "We got so nervous—everywhere we went nobody would help us." "We then thought it was God's will and we did not go anywhere." "I feel the doctors brushed me off." "I feel that the medical profession did not want to be bothered, were impatient and annoyed." "We did not find anyone who sat down and told us what the problem was." "They just push you from one person to another." Is it any wonder then that there were expressions of anxiety, embarrassment, and guilt? As one parent said, "The doctor did not want to be bothered. I was embarrassed to go to his office. I had to sit with other people's children. I was always treated with the attitude: 'Here comes this woman with this child.' The doctor did not like him and did not mince any words about it." Another said, "The majority of professional people we dealt with left us with the feeling that if you had a child who wasn't normal, you should be ashamed of it."

Of the total group of 40, in 30 of the cases studied the parents suspected or were aware of retardation in the first year of life. Of the mongoloid group of 19, in 13 instances the parents were aware of and/or were told of the serious deficiency within the first month. The brain damaged and the etiologically unspecified cases of mental retardation took longer to diagnose. In the brain-damaged group, 12 were suspected of retardation under 1 year of age (3 of whom were known under the age of 1 month) and the remaining 3 took up to 3 years to diagnose. In the cases where no specific cause of retardation was known, 1 was diagnosed at age 20 days, 1 at 8 months, 1 at 1 year, and 1 at 18 months. In the two remaining cases, the epileptic was diagnosed at 10 months and the other was diagnosed as questionable retardation due to emotional factors. Therefore, we must conclude that mental retardation was serious enough to be detected reasonably early in this group of children.

As one would expect, it was the pediatrician who was most frequently consulted first (in 25 instances). This was followed, in order of frequency, by the family doctor in 7 instances, the obstetrician in 3, the neurologist in 1, and the child guidance clinic in 1. In 3 instances the parents "just knew" and did not consult anyone at the time. "Were others consulted and at what ages?" prompted a succession of medical specialists too numerous to record. Illustrative is one parent's comment, "I must have had Billy to over 100 different doctors." Another replied, "I must have spent over $8,000.00 for various consultations to no avail." Unfortunately, parents did not seem to obtain the help they needed early enough to prevent the trauma of endless pursuit of answers to their problems. Perhaps, significant is the fact that the "end of the road" seems to be the child guidance

clinic, psychologist, or psychiatrist, whom the parents finally seek in desperation, usually after the child is 2 years of age. Also significant is the fact that one-half of these patients finally reached these specialists.

"Who really told you?" produced only one significant point, namely, many parents "just knew" or suspected serious pathology long before affirmation by specialists. The author has found that it is not an unusual occurrence in clinical work for a parent to be able to state fairly accurately the intellectual level at which his child is functioning at the time he is seen. What the parents are really asking for is not just a diagnosis, but total handling of the problem.

The question "How were you told your child was retarded?" evoked the most intense responses indicative of the traumatic experiences suffered by so many of these parents. The striking thing that permeated this section was that the different reactions to what parents considered good and poor handling varied according to their own individual needs, so that one is forced to conclude that the most important consideration is the ability of the counselor to individualize, to be sensitive to where the parents are emotionally at a particular time, in other words, to empathize with the parents. Some parents wanted to be told directly as soon as retardation was suspected. A typical comment was, "The doctor was very frank about it. It was very positive and in no way abrupt. We were aware of what the situation was, and we appreciated knowing this." Another commented, "I was told right at the beginning. We were always thankful to the doctor who did tell us." On the other hand, many parents indicated their wish to be prepared gradually, as follows: "The doctor was very tactful. He implied things right along. At first he said she was not holding her head up, not sitting up, etc. Not until two or three years later did he really tell me the child was seriously defective and had to be in an institution. He prepared me well." Another parent reported, "A pediatrician told us the child was retarded. He told us in the nicest way it could be explained. He told us it was far too early to say how much he would progress. We returned for visits frequently. As the child grew older, we were told what the future held." Apropos of this discussion, it should be pointed out that frequently parents inadvertently mentioned the names of the doctors they had consulted (in spite of the request that no names be mentioned). It is of interest to note that a parent would condemn a doctor while another would highly praise the same doctor. This obviously casts no reflection on the doctor but emphasizes the need to individualize each situation. Another observation is that in almost every record there is an admixture of good as well as poor handling, which again emphasizes the premise to handle each situation individually.

Important to note is that, when questioned specifically, only 25 per cent of the parents indicated that their contact with professional people was satisfactory. The most important factor in this regard was that these parents were counseled not only sensitively and directly, but also their questions were answered, particularly those relating to implications for the

future. A typical expression was, "Our family doctor was wonderful. He talked to us for about an hour. He said our child was a dull boy and to give him regular care, but to give him a little bit of extra love. He answered all my questions and told me just what to do. He prepared me well for the future." Another stated, "A psychiatrist told me for the first time my child was retarded. It was a shock, a bitter disappointment, but it was accepted. He told us what to expect and gave us wonderful advice." Another 8 also indicated they were told directly, frankly, tactfully, sensitively, or slowly, but in most instances, questions pertaining to implications for the future were not answered. In 3 cases parents were not informed by anyone, "they j u s t knew."

In 16 instances parents clearly described how poorly they were told with such adjectives as cruel, abrupt, confused, blunt, upsetting, contradictory. The adjectives the parents used are graphically illustrative of descriptions of their experiences, and they reacted to them with such comments as: "They tell you your child is an idiot and everything else. There should be a nice way to tell parents. When they told us roughly, we stopped going." "The doctor said he will never be any good to you or to himself. I told him I was raised with the feeling where there's life, there's hope." "I was told my child was mongoloid without any preparation for it. I thought he was perfectly normal, and it came as a complete surprise. We had just stopped in for a checkup. The doctor said I should have him in an institution because it would be better for the child and everybody else. All I wanted was to get out, I was stunned. My husband was overseas at the time, which certainly did not help. When you think back, you can't believe anyone could be so blunt." Two parents commented that they were told over the telephone: "My husband was told over the telephone that the child was a mongoloid when the child was 4 days of age." "The doctor said our child was a mongolian idiot over the telephone. He acted as though it was your problem, buddy."

Numerous references were made to examinations which were considered too hasty and careless: "It was an assembly line fashion." "The interview was not at all satisfactory. He saw us very quickly and did not even give us the results of the electroencephalogram. He sent us a note and suggested we buy a book he wrote. Good God, we still don't know whether he is epileptic or not." "I didn't have the feeling wherever we took her that they thoroughly examined the child." "The doctor gave her a 3-minute examination and said she was brain injured and threw her out." "The mother knows first of all what the child is. She's around the child all the time. She knows him thoroughly. How can a doctor, who sees a child for one-half an hour, know about the child?"

One other complaint, that was outstanding in the study, was a tendency on the part of professional persons to evade the issue. As one parent said, "The doctors gave me no clue that anything was amiss. In fact, they assured me everything w a s going to be all right."

Other complaints pertained to complicated medical terminology.

As indicated in the preceding section, there are certain generalities that can be made, namely, that parents would want to be handled gently and warmly at all times, in language that they can understand, without evasiveness, after thorough examination and, with enough time to digest the significance of such important material. This was reinforced by the parents in response to the question: "What type of service would you advise for people who are faced with this problem and are just beginning?" The material indicates that they need gentler, more sensitive handling than the usual patient. This is supported quite vividly, as they expressed intense feelings and reactions. Particularly they stressed that their "children be treated as individuals" and that the counselor be interested in their problems. What they seemed to be expressing is the need for more responsible, integrated services in this field. Professional people are becoming aware of this, as special diagnostic centers are developing in various parts of the country. Parents are able and willing to accept the uncertainty involved in diagnosis in an area which is not clear-cut if they could depend on a centralized resource rather than to be left to shift for themselves in an endless search for answers which are not possible.

In the instances where parents indicated the wish for frank, direct diagnosis as early as possible, they felt they could accept the worst if the counselor was compassionate and respected them as parents with strength and dignity. They needed time to take in the extent of their problem, and they needed to work out solutions step by step. Questions did not arise in an organized, crystallized fashion, but gradually as the child grew. As one parent put it, "This is a lifetime thing."

Some of the comments of the parents are indicative of their keen feelings of anxiety and guilt, and it is important to emphasize that this is not resolved simply by articulating it for the parent. One parent said, "I got angry at people who told me not to feel guilty. It only made me feel guiltier." There seems little question that, for many parents, the highest degree of specialized skill is indicated in the area of counseling. If we, as professional persons, really listen to what parents of mentally retarded children say, we can take our clues from them. It was not unusual to find parents express relief as they learned their children could at least be toilet trained and could express such simple needs as to ask for water, etc. As one parent said, "I used to lie awake and pray that my child could say a little word like 'water' because I was so afraid he would be thirsty and could not help himself." It is interesting to note that two parents spontaneously commented that they were relieved in "spilling over to me," although they had innumerable, previous opportunities to talk about their problem.

Two observations worthy of mention were related to terminology. One is that parents showed severe reaction to such terms as idiot, imbecile, and moron, and hoped for terminology that would avoid such negative connotation. Another is their request for simpler explanations in terms they could understand, particularly, practical, tangible suggestions relative to everyday living. Perhaps

we need a greater appreciation of the little achievements of the retarded child and its meaning to their parents. Still another request was for clearer explanations, the full meaning of which they could take in. Parents often interpret such terms as "the child is slow" to mean that the child "will catch up in due time." In my clinical experience I have found that a better way of helping parents to understand what is really meant is to use the word "behind," connoting that the child will not catch up.

A discussion of the material would be incomplete without giving some illustrations of the continuous history of the parents' search for help. Comments taken out of context and categorized cannot possibly present the full meaning of the total impact of accumulated frustrations on the parents on the one hand, and their strength and capacity to handle their problems on the other. Only as we can appreciate and accept this can we be fully helpful in developing adequate services. Two records have been selected to illustrate this: the first one concerns a child diagnosed as mongoloid and the second one a child diagnosed as brain damaged.

Mrs. Martin, the mother of five children, is a warm, motherly person, of limited educational background but, nevertheless, of good intelligence. She is a thoughtful, sincere individual.

She begins as follows: "I knew Johnny was a slow child, but I thought he was a sick child. During infancy he slept for the most part and we couldn't awaken him." Early he was taken to the clinic; however, no mention was made of retardation. "They said he was just sick. He was not a well baby, but would probably pick up, but they never gave me a reason." However, an attendant kept repeating, "If only I had your faith." Apparently this comment seemed so inappropriate at the time that it made an impression on the mother.

When Johnny was about 2 years of age, a doctor was called about another sibling and casually commented that Johnny was mentally retarded. The doctor referred him to the hospital where the opinion was that the child was a mongoloid, very retarded, and that the best thing for us to do was to put him in an institution because he would forget us very quickly and if we had other children, it would have an effect on the whole family, particularly that our children would be embarrassed because of Johnny. On this statement, Mrs. Martin comments, "I thought that was abrupt and cruel."

Mrs. Martin continued, indicating her upsetness over this experience. She said, "After I got home, I wanted to know how retarded he was because I was too upset to ask any questions while I was at the hospital." She returned to her pediatrician because apparently she had a warm relationship with him. He disagreed with the opinion of institutionalization, suggesting that it was the parents prerogative to decide such a drastic move. His opinion was that the child needed the love which could not be received in an institution. He explained Johnny's mentality, cautioning her not to spend any money on Johnny, but to center her financial resources on the other children. The doctor's most meaningful comment, and Mrs. Martin says this with much warm feeling, was, "Remember, when your other children have left, you will always have Johnny." (In response to the question, "Who gave you the most help?" Mrs. Martin unequivocally said it was this pediatrician.)

The parents explored every school possibility without any success until he was 10 years of age when he was accepted in a special class in the public school. He stayed there four years and was withdrawn when the

center closed, and was then placed in another school. According to the mother, considering his limitations, he has made a good adjustment at school. He mixes well with the other children who have encouraged him in this respect. He even writes, spells, and does a little arithmetic. Mrs. Martin feels that the school has been instrumental in giving Johnny confidence, and enabling him to do some of the things normal children are doing. She glowingly describes her relationship with the teacher as "wonderful," particularly the help to the parents in allowing them to sit in class, observe, and learn.

In response to the question "Do you feel that your contact with professional people had been satisfactory?" Mrs. Martin's first point was, "Parents need all the kindness you can give them."

She also felt that parents should know exactly what is wrong as early as possible. If known at birth, it should be told at that time because one can be more helpful to the child. She regretted the information being withheld from her. She described it as "not fair." "It's yours, your baby, you want to know right at the beginning." Mrs. Martin had the feeling that everyone knew that her child was mongoloid except herself. It bears emphasis that she was not informed that the child was a mongol until he was 2 years of age.

She further emphasized that "if there is a ray of light, it should be told." When the pediatrician told her Johnny could reach the mental age of 8, it was helpful to her. "Every word we took hold of."

Still another area of importance is to handle questions pertaining to heredity. The Martins were very much concerned whether to have additional children, and it was with great relief that after repeated contacts with professional people, she finally got her questions answered.

"What type of service would you advise for people who are faced with this problem and are just beginning?" brought forth the seriously traumatic experience of first being told bluntly and insensitively. "I felt it could have been handled a little more kindly. If you can speak to anyone in the medical profession for a while, it's wonderful. If they can't help the child, maybe they can help the parent."

About institutionalization, she commented, "I think too many children like this are put in institutions. It frightens the parents to think of institutions. I don't think an institution should be mentioned at first. Couldn't it wait to see how a child progresses before it is mentioned? I am truly as proud of Johnny as I am of my boy who graduated from college."

The second record is as follows:

This is one of the few situations in which both parents participated in the interview. The Allans are intelligent, fairly young people, in their middle thirties, and have a family of three children. In spite of all of their struggles, their charm and zest for living comes through.

Bobby was about 7 months of age when they had some vague suspicion that all did not seem quite right. They consulted their pediatrician who said that he was a little slow—not responding, not sitting up. "But the pediatrician said nothing to allay my fears, he said Bobby would be all right." Then, with much feeling, Mrs. Allan adds, "He didn't say this because he didn't know—he did know."

After much "badgering," on the mother's part, and insistence that there must be something wrong, they were referred to a neurologist. Bobby was about 1 year of age by this time. The examination showed that he was nearsighted.

Further consultation with two doctors indicated that there was nothing wrong. Mrs. Allan said, "I thought I would work harder and teach him more. Then began the most frustrating period of my life. Trying to

teach a child when it was not possible to teach him was like knocking my head against a stone wall. My heart just aches when I think what we have been through. I pushed him. I spent a lot of time with him. I would try to feed and toilet train him and we got just no place."

The Allans returned to the pediatrician, whereupon they were referred to an orthopedic man. At that time, Bobby was about 1½ years old, and Mrs. Allan estimates his intelligence at about 1 year. The orthopedic man found his feet were quite flat and suggested corrective shoes. He also offered the following advice, "He will catch up, he will be all right." Mrs. Allan, however, felt all was not so rosy because she mentions that at 19 months he was beginning to walk but "still there was not a flicker any place else."

When Bobby was 2 years of age, the family was referred to a psychiatric clinic. Here she describes her experience as "wonderful." The doctor spoke to her at some length and "it was almost a relief for me to hear it. At least I knew where I stood." By this, Mrs. Allan means she had her suspicions confirmed, namely, that Bobby was retarded. However, he was described as being only mildly retarded, with a good prognosis, but the years have proved otherwise. At least she knew she didn't have a normal child.

Mrs. Allan described meeting her pediatrician on the street and berated him for not telling her the truth. His comment was, "You couldn't have done anything about it anyway. I knew that you would find out soon enough." Mrs. Allan emphasized how deeply disturbed she was during that time.

Although Mrs. Allan felt she was reasonably well handled by the psychiatrist, her questions were not answered. When questions arose regarding other children, Mrs. Allan consulted her pediatrician and he advised her against having another child. Their obstetrician, however, encouraged her to have another one. She subsequently became pregnant, and describes this period as one of great fear of having another retarded child. In the sixth month of pregnancy she contracted mumps, and "nearly went crazy." "The baby was wonderful. Anyway it had a happy ending."

At about 3½ years of age, Bobby had his first convulsion, his condition was followed at the seizure clinic, where he was put on medicine for convulsions. The parents *were* told nothing about his condition, and were critical of the fact that he did not have a complete work-up. They ". . . were not even told what the EEG showed."

There was further pursuit of medical exploration until finally they consulted a psychiatrist. The psychiatric consultation was described as being reasonably satisfactory, although the psychiatrist was "cold, he told us the brutal facts. At least I could start living after that rather than just hoping. Even so, he was optimistic." He recommended institutionalization, but the parents indicate their disapproval of this with much vehemence. The psychiatrist also pointed out that they were concentrating too much on the retarded child to the exclusion of the normal sibling. The indications are that they could accept this.

In answer to the question, "Was your contact with professional persons satisfactory?" the response was "absolutely not." Then they added, "In fact, we have lost a great deal of respect for the medical profession; we have had nothing but frustration every place we have turned."

"What type of services would you advise for people who are faced with this problem and are just beginning?" brought the immediate response, "Gently, but the truth." Mr. Allan felt that the counselor should evaluate the type of parent and the intellectual capacity of the parent, have a few visits with them if necessary, and handle them accordingly. They both

agreed that the parents should be informed just as soon as the doctor knows. He said, "The attitude is of paramount importance. If the parents sense sympathy in the professional person and willingness to understand, this has a great deal of meaning. After all, most parents want to respect their doctor."

One further comment revealed the magnitude of the burden for parents when Mr. Allan said, "After all, you have a whole lifetime to worry about this, and you can only take it by degrees."

The discussion of the questions of institutionalization produced much negative response on the part of the parents, especially when the counselor had no direct knowledge of the resources but, even more important, little understanding of the family and indiscriminately advised it as a solution. Illustrative are such comments as: "They all spoke of institutional care as though that was the only thing we could do. They acted as though we had no choice." "If the child can be cared for at home and is not a burden on other members of the family, then they should keep him. I look at the happiness Billy has given us—he is so sweet and kind. The other children in the family adore him." "I honestly think that Tommy would not have gotten anywhere in an institution. There is no difficulty in having him at home." Without exception these parents wanted what was best for their children. They wanted to know whether the resources would help their children to achieve their capacities, however meager, and help them grow up as well as possible considering their handicaps. When necessary, they can come to terms with institutional care if that is the soundest way of helping their children. They asked whether their children need more than their share to enable them to assimilate whatever training and education are available. Also, they are able to provide the tender, loving care to make this possible. So many parents cannot be interviewed without the interviewer being greatly impressed with their love for their retarded children, and their ability to accept and handle frustration. It is important to note that in 21 of the cases institutional care was recommended early, but in only one was it followed through. The obvious conclusion is that they were not ready or interested in this solution to their problem.

It is significant to note that there is important research going on in the field on the families who can best use institutional care for their retarded children. One study, still in progress, considers the effects of a severely retarded child on family integration, the results of which can be of help to counselors in evaluating the kind of family who can keep their child with them and those who might best be directed toward institutionalization.

Apparently there has been more change in the attitudes of society toward retarded persons than we realize. The prevalent assumption has been that families cannot accept too much difference and that the higher the cultural and intellectual achievement, the less possibility there is for the retarded child to be cared for at home. This is not supported by this study. On the contrary, a place has been found for these children in their families, neighborhoods, and schools. I do not believe that it is being too omniscient to say that many of these children have gotten as good a start

in life as is possible under the circumstances. I should doubt that anyone would challenge the fact that the institutionalized child does not have his emotional needs met.

Needless to say, parents spoke glowingly of the local state Society for Retarded Children. They have found a way to share their experiences, to be supportive to each other, to resolve their feelings of difference, and, most important, to speak for retarded children and crusade in their interest. This has been an invaluable group therapeutic experience for many parents, an important factor in enabling families to live more comfortably with these children and to be helpful to them. They have proved parents need to be no longer isolated as individuals and families, with the serious emotional problems which set them apart from the rest of the world. These parents have paved the way for community understanding and acceptance of the problem, and have achieved an important role in community welfare by speardheading the need for specialized services in education, recreation, parent education facilities, and in programs of financial aid. They have discovered so much for themselves that they want to share their experiences and to be helpful to others.

THE VECTORCARDIOGRAM OF MALNOURISHED CHILDREN DURING THE FIRST MONTHS OF LIFE

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IT HAS been claimed that vectorcardiography affords a better visualization of the electrical forces generated within the heart than scalar electrocardiography, especially in respect to right-sided heart lesions.[1] As a rule, the fundamentals of such investigations have been based on studies on adults, or on children presenting either congenital heart disease or a normal cardiovascular apparatus and body build.[1-4]

During the period of life which immediately follows birth, the heart works harder than in latter stages because of immediate extrauterine circulatory adjustments. Furthermore, a "physiological" right ventricular preponderance is said to occur from an electrical point of view.[5] This means that in what concerns the balance of electromotive forces, the heart behaves like that of an older child or an adult with pathological right ventricular hypertrophy. Certain investigators, as Elek and associates[5] and Doll,[6] have analyzed vectorcardiographically the transition from the neonatal period to a following stage when the "physiological" preponderance no longer exists. However, their study did not include malnourished children, nor did it emphasize certain abnormalities displayed by the repolarization loops, that is, the T loops.

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MATERIAL AND METHODS

During the summer of 1957, we obtained vectorcardiograms and electrocardiograms from 54 malnourished, diarrheic children admitted to the Children's Hospital. Their ages were under 6 months, and their weights ranged from 4½ to 10 pounds. All infants had been underweight since birth, and the population was so diverse that weight could not be related exclusively to age, as it was possible for older children to have a lesser weight than younger ones. It is important to note that recordings were usually taken after diverse intravenous solutions were administered. For comparison with the former group, the tracings and loops from 22 normal children of average height and weight, seen in the outpatient department, were studied. Their ages ranged from 1 day to 6 months, and their weights from 7½ to 15 pounds. Clinical studies and x-ray films in both groups revealed no evidence of heart disease.

All vectorcardiograms were taken with the Frank[7] method of electrode placement, as originally described by

this author for adults and by Castellanos and associates[8] for children. Briefly, it consists of a five electrode system (size: 2 by ¾ inches) centered on the fifth interspace, and applied on the following regions: E, front midline; M, back midline; I, right mid-axillary line; A, left mid-axillary line; and C, at a 45-degree angle between E and A. Two additional electrodes (H and F) were placed on the neck and left leg, respectively. The cables proceeded from the patient into a small insulated box which included the appropriate resistors, as conceived geometrically in the image torso by Frank[7] so as to obtain "ideal" dipole components for the subject under study. The corresponding three outputs representing three potential differences (horizontal, frontal, and sagittal) were fed into the Sanborn vectorcardiograph, so that the pictures could be obtained directly from the oscilloscope screen by means of a Dumont 295 Camera loaded with Tri X Kodak films.

In many cases the loops were best visualized after the administration of 0.05 Gm. of secobarbital sodium by rectal route. Whenever the technique outlined above was employed, the recording of the vectorcardiogram was not more difficult than when performing routine electrocardiograms on children of the same age.[8]

RESULTS

Although three-plane vectorcardiography offers a complete study of cardiac electromotive events, most authors, following Grishman,[1] have correctly assumed that the horizontal loop, particularly in children, displays the most important data. This is because of the obvious relation between this plane and the precordial leads, which have been found for many years to be of great help in the diagnosis of heart disease. Such a relation is *schematically* illustrated in Fig. 1, where the QRS complex of

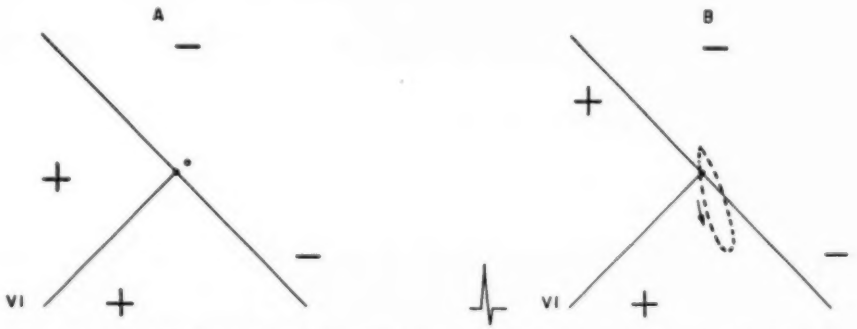

Fig. 1.—The derivation of the QRS complex of precordial Lead V_1 from the horizontal vectorcardiogram.

scalar Lead V_1 is derived from the horizontal loop. As the latter represents a transverse section through the heart at the level of the electrical center, V_1 is located, as expected, somewhat to the right of the front midline. A line is then drawn from point V_1 to the point where all dipoles originate (center of cardiac electrical

activity); and a second line, perpendicular to the first, is also drawn. In this way the electrical field is divided into two parts: a positive one located between V_1 and O; and a negative one, on the other side of the perpendicular to V_1. All the electrical forces placed in the positive side of the field will yield a positive deflection in V_1; and vice versa, while those located in the negative side of the field will produce a negative deflection (S wave), which is proportional to the magnitude of the vectors.[4] On the right side of Fig. 1, labeled B, a loop is presented which produces an Rs complex in V_1 because of its greater (and initial) part being located in the positive side of the field, and only a terminal, smaller part in the negative side. The direction of inscription in this, and in all illustrations, is represented by the head of an arrow. However, this relation is not absolute for certain discrepancies are obvious[7] due to the underlying vectorcardiographic system.

Normal Children.—During the immediate neonatal period, the horizontal loop is inscribed in a clockwise fashion, being placed anteriorly and to the right, so that a tall R wave is observed in Lead V_1 (Fig. 2, left). Those vectorcardiograms, except for voltage criteria, were indistinguishable from those of older children or adults with pathological right ventricular hypertrophy. At about 26 days, the loops changed in contour presenting a figure-of-8 configuration[5] due to the rotation of medial forces, but, always with the location of the crossing anterior to point O. These loops were also observed in older children with right ventricular hypertrophy and moderate to high right ventricular pressure.[8] Finally, at about 36 or 38 days, a change in morphology occurred and the loops were then inscribed in an anticlockwise fashion (representing the normal infantile pattern) (Figs. 2, right, and 3). When projected on V_1, those vectorcardiograms also yielded prominent R waves.

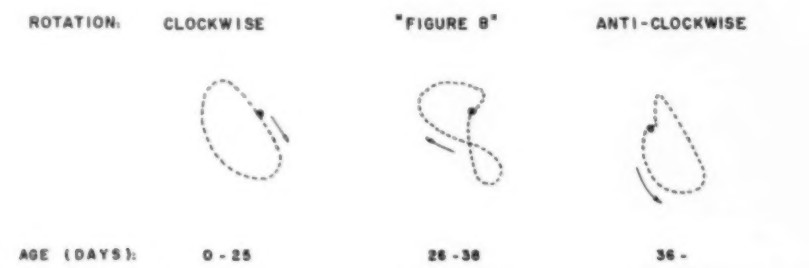

Fig. 2.—Normal QRS loops. Vectorcardiographic transition from neonatal to infantile pattern in the horizontal plane of infants with normal weights for the local population (Frank system).

The analysis of the T loops revealed that they had a very anterior location during the first two days of life (from +35° to +90°) and, hence, a positive T wave appeared in V_1 (Fig. 4). After that age, they shifted to a posterior position during the whole period under study (+35° to –60°). However, the usual location was between –15° to –60° (Fig. 5).

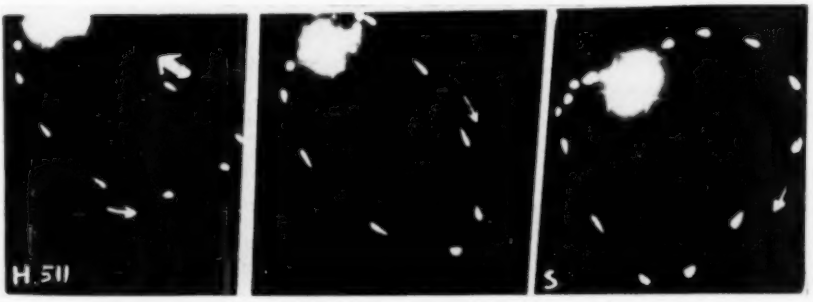

Fig. 3.—The spatial vectorcardiogram (QRS loop) of a normal 50-day-old child. It can be seen that rotation is clockwise in the horizontal plane (left, H.511).

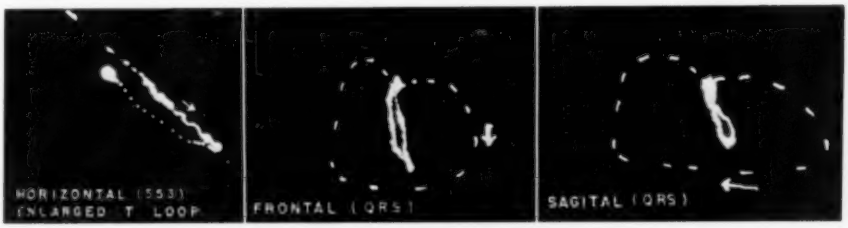

Fig. 4.—The spatial vectorcardiogram of a normal 12-hour-old infant. The enlarged horizontal T loop has a clockwise rotation and a direction close to +50°, so that a positive T wave was recorded in precordial Lead V_2. The horizontal QRS loop (not shown) also had a clockwise rotation (Fig. 2, left).

Fig. 5.—The vectorcardiographic T loop of a normal 50-day-old child. In the horizontal plane (left) the inscription is anticlockwise, and the direction close to −30°. The vectorcardiograms were recorded at increased amplification.

Malnourished Children.—In this group it was noted that clockwise loops existed not only during the first month of life, as occurred with normal cases, but persisted on several occasions until the one hundred fortieth day. Also, a prolonged persistence of figure-of-8 loops was found, for they were even observed in 6-month-old infants (Table I). As we were dealing with malnourished children, it seemed appropriate to try to establish a relation between the type of loop and body weight, as Elek and his colleagues[5] did. Indeed this relation existed, for Table II shows that the weight of clockwise vectorcardiograms was, on the average, less than the ones with figure-of-8 morphology. However, there was a significant degree of overlapping. On the other hand, anticlockwise rotation first appeared by the fortieth day, persisting to the one hundred eightieth day. This morphology generally corresponded to the infants with higher weights (Table II).

Finally, when the mean direction of the T loops was analyzed, it was appreciated that in 32 cases (62 per cent) it was placed between 0° and +90°, a location attained by children of all ages and weights, obviously not related to these parameters. Similarly, the loops with the usual location (0° to −90°) also belonged to children of all ages and weights (Table III). These findings contrast markedly with those of normal children.

TABLE I. RELATION BETWEEN AGE (IN DAYS) AND LOOP ROTATION IN THE HORIZONTAL PLANE

LOOPS	AVERAGE	RANGE
Clockwise	63	2-140
Figure-of-8	71	30-180
Anticlockwise	97	40-180

TABLE II. RELATION BETWEEN WEIGHT (IN POUNDS) AND LOOP ROTATION IN THE HORIZONTAL PLANE

LOOPS	AVERAGE	RANGE
Clockwise	5.15	4-8
Figure-of-8	6.70	5-8.5
Anticlockwise	8.20	6-10

DISCUSSION

With the Frank system of vectorcardiography, it was seen that in normal children the transition from "physiological" right ventricular preponderance occurred more or less at the same age as it does when the Cube system was employed (26 to 40 days).[5] Originally, Elek thought that this transition was exclusively related to the anatomical investigations which emphasized that there existed only slight differences in the weight of the right and left ventricles during the first month of life.[5] This author believed that it was not until after the first four weeks that the left ventricle showed a definite tendency to outgrow the right. However, recent re-evaluation of the anatomical changes by Sala Panisello and coworkers[10] and Sodi Pallares[19] have

TABLE III. RELATION BETWEEN AGE (IN DAYS), WEIGHT (IN POUNDS), AND T LOOP LOCATION IN THE HORIZONTAL PLANE

T LOOP LOCATION	AGE		WEIGHT	
	AVERAGE	RANGE	AVERAGE	RANGE
0° to +90° (32 cases)	125	1-180	5	4.5-10
0° to −90° (22 cases)	101	1-180	6	4.5-10

shown that this is incorrect because, occasionally, during the first postnatal days the right ventricle did not overweigh the left. Nevertheless, a disturbed "physiological" right ventricular/left ventricular relationship exists at this age, similar to the one present in older children or adults with moderate, pathological right heart disease, specially congenital defects, is almost surely absent. But such data cannot be gathered from Lead V_1 because, as stated by Grishman,[1] differently inscribed loops (one representing a normal case and the other right ventricular hypertrophy) can yield the same unipolar morphology (Fig. 6).

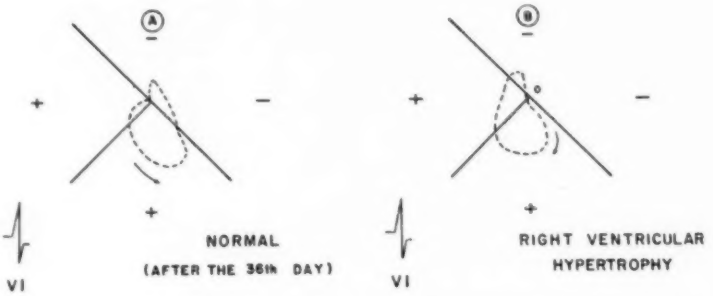

Fig. 6.—Schematic illustration showing how different inscribed horizontal QRS loops can produce the same unipolar morphology.

ventricular hypertrophy. It thus explains the disturbed balance of electromotive forces, which, in turn, are responsible for the clockwise inscribed vector loops as well as for the tall R waves in scalar Lead V_1. It is evident that a heavier right ventricle is not always the only factor responsible for the changes mentioned above.

A well-known fact of electrocardiography in infancy is the occasional impossibility of differentiating a normal from an abnormal record in the first two months of life, for both can present similar axis deviation and similar morphologies in the precordial leads.[4] However, this distinction may be possible in normal but definitely not in malnourished children, as can be seen from the inspection of the horizontal plane. If the loop is inscribed in an anticlockwise fashion,

One main characteristic of malnourished children was the finding of clockwise loops related not only to age but also to weight, a possibility anticipated by Elek and co-workers,[5] in 1953, who, nevertheless, did not make a systematic observation (Tables I and II). Evidently, the patients studied had a much lower weight than average infants of the same age. In the infants who weighed the least it seemed reasonable to assume that there occurred a delayed transition from "physiological" right ventricular preponderance, a phenomenon undoubtedly linked to a delayed progression of the usual right-to-left ventricular ratio, which remained at an earlier stage of development. Such abnormal persistence of clockwise loops was definitely ascribed to the material under consideration, that is, children who

had been badly nourished since birth had never attained a normal body build.

Furthermore, in Table III it can be observed that in the abnormal group the distribution of the T loops (and T wave polarity in V_1) was definitely not related to age or weight.

As heart disease was not found in any of the children studied, it seemed logical to assume, as Rosen and Gardberg[17] did, that right ventricular hypertension was not the cause of the anteriorly located T loops (and of the positive T waves in V_1) which were sometimes seen. Obviously, they must represent primary changes in repolarization, and it is interesting to note that no evidence of these alterations was found in the studies of Muñiz and Amable.[11] Their group analyzed 53 electrocardiograms of diarrheic children during an epidemic which took place several years ago in Havana. Unfortunately, their material and methods differed from ours in several aspects: (1) children up to 3 years of age were included; (2) infants were not necessarily malnourished; and (3) the records were obtained mainly before treatment and/or immediately before discharge, with no tracings in between.

Moreover, at the Children's Hospital of Havana (where Muñiz and Amable also performed their investigations), fluid therapy is inconsistent in its electrolyte content. Specifically, the potassium content can be very high or completely absent. This assertion is made because it was originally thought that a modification of the intracellular to the extracellular potassium could explain the pathological repolarization loops (and the corresponding T wave positivity in V_1).

However, as they were seen in patients with normal as well as with low serum potassium, another explanation had to be sought. For instance, the vectorcardiogram presented in Fig. 7, taken from a 48-day-old child after intravenous potassium-containing fluid therapy, is an example of a figure-of-8 QRS loop, with a very anteriorly placed T wave. The precordial electrocardiogram from the same patient is shown in Fig. 8 (upper tracing); as expected, all T waves are positive in V_{4R} and V_1. The Q-T interval, a measurement not appreciated from conventional vectorcardiography, is 0.44 second, applying Bazett's formula. At the time, serum potassium was 5.2 mEq per liter and calcium 4.9 mEq per liter.

In the lower tracings, obtained a week later, T waves in right precordial leads are now inverted, adopting the normal morphology for this age, and the T loop has reverted to a posterior position (not shown). It is to be noted that the duration of the Q-T interval has remained practically unchanged (0.43 second) as well as serum potassium (4.6 mEq per liter) and calcium (4.8 mEq per liter).

The electrocardiograms in Fig. 8 do not suggest the existence of potassium disturbances. Also, the duration of the Q-T intervals, slightly prolonged according to Bazett, but within normal range according to Ziegler,[12] is nonspecific, as these measurements are when borderline. If considered prolonged, they would indicate hypocalcemia. The finding of a normal serum calcium could be explained on the basis of low ionized calcium. Another explanation for a

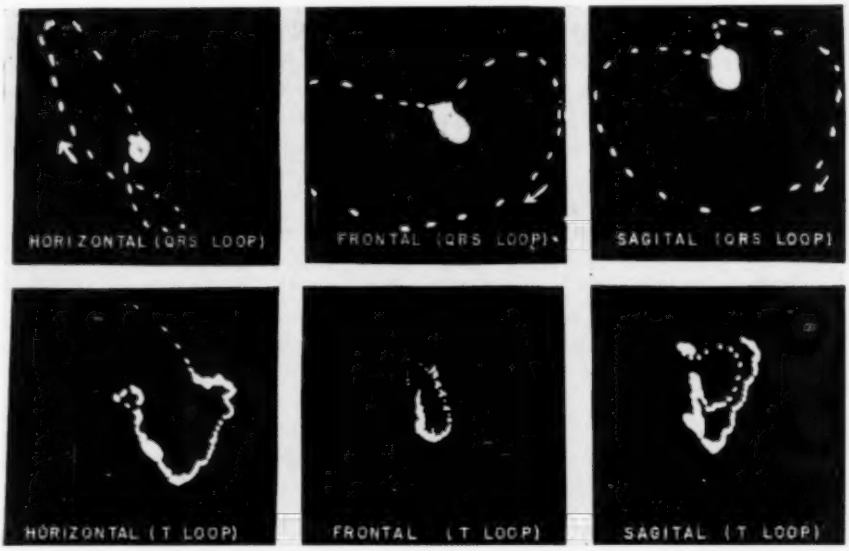

Fig. 7.—The vectorcardiogram of a 48-day-old malnourished child (weight 6 pounds). The horizontal QRS loop presents the so-called figure-of-8 rotation, and the T loop has a location close to +75°.

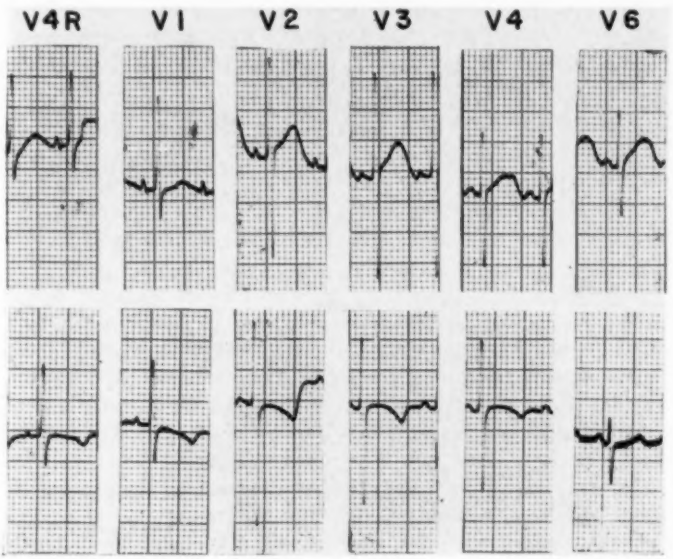

Fig. 8.—Above, June 14, 1957, precordial leads of the same patient whose vectorcardiogram was presented in Fig. 7. Positive T waves can be seen in the right precordial leads. Below, June 21, 1957, precordial leads from the same patient taken one week later, now showing an inversion of T waves in the right precordial leads.

prolonged Q-T interval could be the acidosis which the child did have at the beginning of the disease,[13] but this possibility seems improbable.

Our present experience does not allow us to state whether the anteriorly oriented horizontal T loops (and positive T waves in V_1) have a similar pathogenesis to those found in certain other interesting investigations. Some years ago, Goldberger and his coworkers[14] administered potassium salts to normal children with the usual T-wave inversion in the right precordial leads and observed how these became positive or less negative. They estimated that the infantile pattern was due to hypokalemia, an assumption which, definitely, has not been confirmed.[12] On the other hand, in our material abnormal repolarization complexes were observed when the electrocardiogram and vectorcardiogram displayed definite signs of hypokalemia. This is shown in Fig. 9, obtained from a 56-day-old malnourished patient whose serum potassium was 2.9 mEq per liter and calcium 4.8 mEq per liter. The records, taken after intravenous administration of glucose (without potassium) solutions, show the following: (1) a u wave taller than the T wave in V_1 and V_2; (2) flattening of the S-T segment in the same leads; (3) isoelectric T waves in V_1; and (4) a Q-T interval measuring 0.33 second (rather short, but still within normal range,[12] yet contrasting with the values shown in Fig. 8).

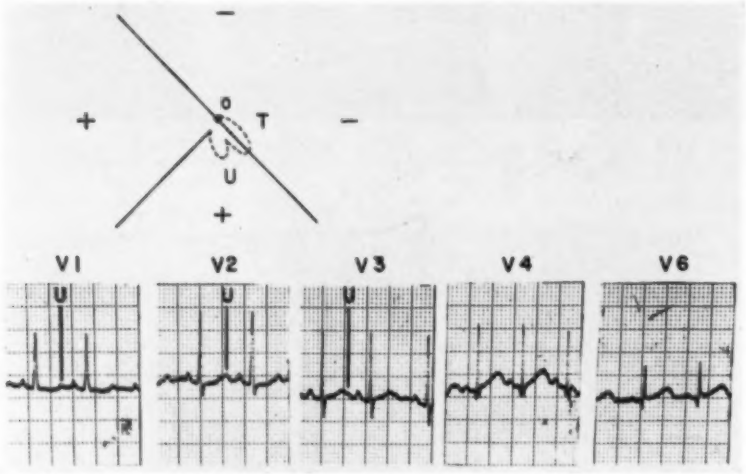

Fig. 9.—Horizontal vectorcardiogram (schematic T and u loops) and precordial electrocardiogram of a 56-day-old malnourished infant (weight 5½ pounds) who displayed electrolyte and electrocardiographic signs of hypokalemia.

These electrocardiographic changes are to be considered typical of hypokalemia, as stated recently by Surawicz and associates.[13] Beyond doubt, they have their counterpart in the vectorcardiogram, as seen in the diagram at the top of Fig. 9: (1) a u loop after the T loop; (2) an open T loop, responsible for the existence of the S-T changes[1]; and (3) an anteriorly placed T loop (+35°).

It is to be stressed that Rosen and Gardberg[17] were the first to describe positive T waves in the right precordial leads of small children without right ventricular hypertrophy, but they did not state the clinical diagnosis, electrolyte values, or body build of the patients studied.

In a preliminary report, Lepeschkin and his colleagues[15] favored the electrolyte theory in explaining the genesis of the positive T waves seen normally in V_1 during the first hours of life. Such a phenomenon was attributed to the high plasma potassium content usually present during that period (caused to a large extent by disintegration of erythrocytes expelled from the placenta during birth) and not necessarily to an elevated right ventricular pressure, which has been shown by other investigators to exist not only during one or two but during several days after birth.[18, 20]

On the contrary, Ziegler's[16] report suggested the strain theory as more valid, for this author emphasized the similarity between the neonatal changes with those of older children with congenital heart disease and high right ventricular pressure.

The clarification of the latter discussion is beyond the scope of this paper, but it is stressed that anteriorly located horizontal repolarization loops (and positive T waves in Lead V_1) are observed in different conditions, some pathological, some "physiological," but, nevertheless, not always linked to right ventricular hypertension.

SUMMARY

The vectorcardiograms of malnourished infants were found to be different from those of normal infants. In the latter group, clockwise QRS loops in the horizontal plane were present from birth to the twenty-fifth day of life, and transitional (or figure-of-8 loops) from the twenty-sixth to the thirty-sixth day. Thereafter anticlockwise loops, representing the usual infantile pattern, appeared. The orientation of the repolarization complexes was very anterior for the first 24 or 48 days (yielding positive T waves in V_1), but later it changed to a posterior position ($-15°$ to $-90°$) throughout the period of time under study.

On the contrary, in the abnormal group it was noted that clockwise loops were related not only to age, but also to weight. That is, on the *average*, infants with the lower weight showed a persistence of that morphology beyond the usual age; a phenomenon probably due to a delayed progression of the usual left-to-right ventricular ratio in malnourished children.

Finally, it was clear that T loop location was not related to age or weight, thus representing primary changes in repolarization. Although the most anteriorly placed ones were occasionally seen after the administration of intravenous solutions (sometimes containing potassium salts), their presence in cases displaying definite plasma and electrical signs of hypokalemia favors the assumption that potassium changes, per se, were not responsible for these abnormalities. However, they are not necessarily due to right ventricular hypertension as previously considered.

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IS THERE A RHEUMATIC CONSTITUTION?

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THE association of hemolytic streptococcal infection with rheumatic fever emphasizes the importance of host factors. While hemolytic streptococcal infection is widespread, the incidence of rheumatic fever among individuals infected with streptococcal disease is low, even when untreated.[1] This has led Galdston[2] to suggest that "it is not the germ, nor the infection, that is crucial in the pathologic constellation of rheumatic fever, but rather the constitution of the victim." The purpose of this study is to evaluate the various physical characteristics of what has been called the "rheumatic type" of constitution.

Physical Appearance.—The most obvious question is whether the patient may be distinguished by gross physical characteristics much as the prematurely gray, blue-eyed Nordic type is known to have a proclivity for pernicious anemia. Despite the development of various technical procedures, or perhaps because of it, clinical aids in bedside diagnosis are particularly welcome.

Numerous authors have been concerned with hair and eye color in rheumatic fever. Levine[3] is convinced of a susceptibility among red-haired children. Shrubsall[4] found a preponderance of the pure blond type among rheumatic subjects. Swift[6] and Honeyburne[5] thought children with dark hair and eyes were more susceptible. Hill[7] and Irvine-Jones[8] found no particular preponderance of hair or eye color.

Using the classification of Hill,[7] 103 rheumatic subjects were classified as to hair and eye color. The results are shown in Table I.

As may be seen in Table I, no hair or eye color predominated in this series of patients with rheumatic fever. Unlike the observation of Levine, red-haired children were a minority in this series.

In the course of examining the patients for eye color it was noted that 31 of the 103 patients, or 30 per cent, had the pink, injected sclerae described by Levine. This was, however, comparable to the incidence in a control group of acutely ill nonrheumatic patients in which 27 per cent of 100 patients had injected sclerae.

Lichtwitz[9] has described blue sclerae as being characteristic of the dysmesenchymatous patient he believes to be prone to rheumatic fever. Blue sclerae were found in only 8 of the 103 patients in this series, an incidence of 7.8 per cent.

Racial Descent.—Rheumatic fever is endemic in all countries and among all races.[10] Although it prevails everywhere, it has an uneven distribution

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over the hemispheres and, in fact, within the borders of individual countries. This variation within countries is apparently related to climate, topography, and population intensity[11, 12] rather than to racial stock or strains.

Table I

HAIR COLOR	NUMBER OF PATIENTS	EYE COLOR	NUMBER OF PATIENTS
Dark Brown	12	Dark brown	29
Medium brown	21	Hazel brown	24
Light brown	24	Deep blue	23
Blond	22	Pale blue	24
Black	21	Green	3
Red	3		

Of 204 patients with a history of rheumatic fever, there were 76 who had both parents of the same national extraction. The racial distribution of these patients is shown in Table II.

Table II. Racial Extraction of Rheumatic Patients

RACE	NUMBER OF PATIENTS
Negro	18
Irish	13
Polish	11
Italian	9
Slavic	6
English	6
Scandinavian	4
French	3
Jewish	3
Puerto Rican	3
Total	76

A total of 128 of the rheumatic subjects had parents of mixed or dissimilar national extraction.

These findings agree with those of Wilson,[13] that there is no definite evidence of racial susceptibility to rheumatic fever. Wilson found 32 per cent of the patients in her series to be of Irish extraction, but attributed this to the predominance of Irish families in the community served by her clinic. Stroud and associates[20] and Coburn[21] also mention an increased susceptibility among the Irish. It is interesting to note that the reduced incidence of rheumatic fever among Negroes reported by Wood and associates[14] and White and Faulkner[15] is not supported in this group of rheumatics, among whom Negroes are the largest single racial group.

Body Build.—It has been reported by Lichtwitz[9] that rheumatic fever is common among asthenic body types and uncommon among pyknic body types. To test this thesis the body types of 200 rheumatic children were evaluated by the Wetzel grid. This method was used rather than the more exact anthropometric method. When the height and weight were plotted on the Wetzel grid, it was found that the majority were well proportioned with a paucity of both the asthenic and hypersthenic types. Results are shown in Table III.

Table III. Wetzel Grid Position of 200 Rheumatic Patients

GRID DESCRIPTION (AFTER WETZEL[16])	NUMBER OF PATIENTS
A_4 (obese)	8
A_3 or A_2 (stocky)	29
A_1, M_1, B_1 (good)	103
B_2 (fair)	28
B_3 (borderline)	24
B_4 (poor)	8

Hyperextensibility of Joints.—The increased mobility of the joints in

rheumatic subjects was first described by Wiesel.[17] He attributed it to a dysgenesis of all mesenchymatous tissues of the body. Levine[3] has directed attention to the fingers as being most demonstrative of this hyperextensibility. Dreyfus[18] has described the rheumatic hand further as being slender, with tapered fingers, having a periarticular pigmentation in the area of the interphalangeal joints as well as a pronounced hyperextensibility. Callegarini[19] has carried this observation farther and measured the angle of extension at the metacarpophalangeal joints in rheumatic and control groups.

The simple hinged device described by Callegarini was employed in this study to measure the angle of extension of the metacarpophalangeal joints. The device consists of a wooden pattern of the forearm with hinges at the level of the metacarpophalangeal joints. The maximum extension of the fingers without pain is measured as shown in Fig. 1. The angle of extension is measured with a goniometer considering the flat position of the hand as zero. For uniform comparison, all measurements were done on the left hand. The results of the measurements are shown in Table IV.

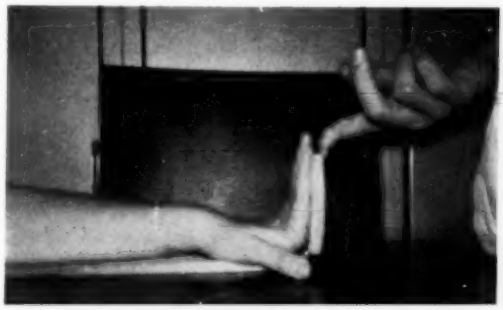

Fig. 1.

Table IV. Angle of Extension of Metacarpophalangeal Joints

Age in Years	Number of Points	Active Rheumatics		Inactive Rheumatics		Controls	
		Average in Degrees	Standard Deviation (Plus or Minus)	Average in Degrees	Standard Deviation (Plus or Minus)	Average in Degrees	Standard Deviation (Plus or Minus)
4	5	93	7	94	5	85	3
5	10	90	5	88	9	80	2
6	12	86	8	88	6	73	8
7	18	88	6	85	12	76	7
8	13	84	11	82	9	69	11
9	16	84	9	86	6	71	4
10	9	85	4	84	5	65	6
11	5	82	2	80	3	64	7
12	4	77	7	82	3	64	5

The difference in degree of extensibility between rheumatic and control groups is shown graphically in Fig. 2. There is a constantly greater degree of extensibility in both the active and inactive rheumatic groups as compared

to the control group. This increased extensibility ranges from 8 to 20 degrees when comparing active rheumatics to controls, and from 8 to 19 degrees when comparing inactive rheumatics to controls. In all groups the degree of extension decreases with age. The fact that both active and inactive rheumatic patients demonstrate this hyperextensibility would lend support to its being a constitutional feature rather than a result of acute disease.

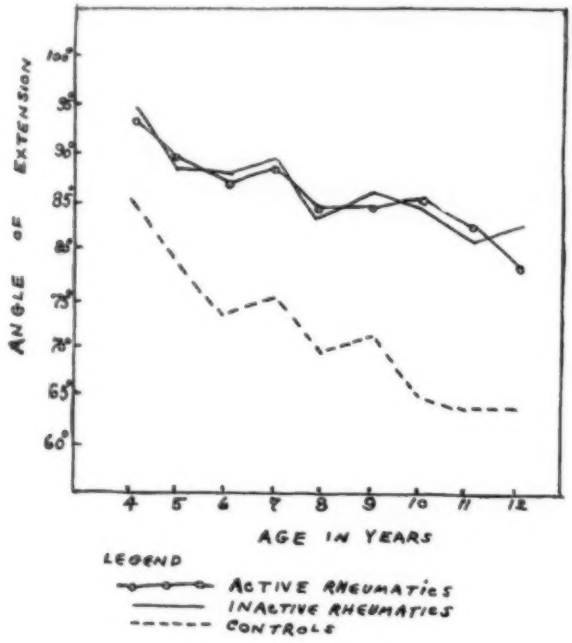

Fig. 2.

Skin Color.—The proper evaluation of complexion as a constitutional feature was complicated by such factors as hormone-induced skin changes, cardiovascular disease, anemia, and prolonged lack of exposure to ultraviolet. The one characteristic of the skin which predominated among patients with active rheumatic fever was pallor. Fifty-four of 103 patients with active rheumatic fever, or 52.4 per cent, showed a definite pallor. The fact that this was an effect of the disease rather than a constitutional feature is suggested by the fact that only 18 per cent of 100 patients with inactive rheumatic fever showed pallor.

Blood Group.—The association of certain blood groups with a predilection for certain diseases has been claimed in various studies. Koster and his co-workers[22] have shown a preponderance of type A blood among patients with gastric carcinoma, and Aird and co-workers[23] found more patients with type O blood among patients with an ulcer than among controls. Wilson[13] found the distribution of blood

types among rheumatics to be the same as controls, but Buckwalter and associates[24] claim an increase of type O among rheumatics as compared with the general population.

Blood groups were determined in 200 active and inactive cases of rheumatic fever. The distributions are shown in Table V. The distribution of

TABLE V. BLOOD GROUP DISTRIBUTION AMONG 200 PATIENTS WITH A HISTORY OF RHEUMATIC FEVER

BLOOD TYPE	NUMBER OF PATIENTS	PERCENTAGE
A	76	38
O	87	43.5
B	29	14.5
AB	8	4.0

blood types shows no significant statistical difference from that described in the general population by Mourant.[25]

Salivary Secretor Status.—It has been shown[26] that approximately 80 per cent of the human population secrete ABO substance in their saliva. Virtually all persons who do not secrete ABO substance do secrete the Lewis substance in their saliva.[27] Glynn and co-workers[28] have shown an increased percentage of ABO nonsecretors among a large group of rheumatic subjects. They suggest that the Lewis substance secreted by the ABO nonsecretors may act as a haptenic material adsorbed onto the hemolytic streptococcus, thereby rendering the streptococcus more capable of invasiveness and the ability to set up the rheumatic hypersensitivity state. The hypothesis is proposed as an explanation for the fact that only a small percentage of untreated streptococcal infections result in rheumatic fever. The hypothesis is particularly interesting in view of the fact that ABO secretor status, like rheumatic fever,[29] is a genetically determined condition.

The salivary secretor status was determined in 50 patients with rheumatic fever. Thirty eight, or 76 per cent, were secretors and 12, or 24 per cent, were nonsecretors. Although the group is too small for statistical analysis, it is of interest that the percentage of nonsecretors is slightly higher than expected. Further investigation of a larger group, including a family study, is anticipated.

DISCUSSION

A previous study[29] has called attention to the importance of hereditary factors in the family incidence of rheumatic fever as well as the role played by a predisposing unfavorable environment. It would be of inestimable value to the clinician given the responsibility of observing the unaffected members of a known rheumatic family or a segment of the population living under predisposing environmental conditions if he could recognize certain constitutional features in a minority of patients which would alert him to their need for special attention.

The spread of rheumatic fever through families as described by Paul[30] points out the need for recognition of susceptibles in known rheumatic families. Secondary cases in families tend to appear in senior siblings. This would indicate that a preliminary period of sensitization or immunological maturation is necessary before the host develops susceptibility. The genetic or environmental factors are not concentrated in a short space of time but act over years. Constitutional features which would be recognizable by physical examination or simple laboratory

screening might aid the attending physician during this prolonged period of developing susceptibility and enable him to institute prophylactic measures.

The one positive constitutional feature brought out in this study is hyperextensibility of the joints. The hyperextensibility of the joints may conceivably be an expression of some underlying biochemical abnormality of the connective tissue.

SUMMARY

1. No characteristic hair color or eye color was found among patients with rheumatic fever.

2. Pallor of the skin occurred in 52.4 per cent of patients with acute rheumatic fever but was not a prominent feature in inactive rheumatic subjects.

3. No evidence of racial susceptibility to rheumatic fever was found in this study.

4. Most patients with rheumatic fever have a well-proportioned body build with a paucity of both the asthenic and hypersthenic body types.

5. A definite hyperextensibility of the metacarpophalangeal joints was demonstrated in both active and inactive rheumatics as compared with controls.

6. Blood group distribution among rheumatic subjects was not statistically different from that in the general population.

7. In a small group of rheumatic patients, there were 24 per cent who were nonsecretors of ABO substance in the saliva. This is slightly higher than the expected percentage in the general population. The possible relationship to the pathogenesis of rheumatic fever is discussed.

I wish to thank Dr. Hugh McCulloch of the Montgomery Spastic Children's School for his criticism of the manuscript. I also wish to thank Dr. S. T. Winter of Rambam Hospital, Haifa, Israel, for many helpful suggestions.

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CARDIOVASCULAR SURGERY IN A CHILDREN'S HOSPITAL

II. Cyanotic Lesions. A Review of 193 Operations

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AT THE Children's Hospital of Philadelphia, 434 cardiovascular operations were performed on 428 patients during the period of May, 1947, to July, 1958 (Table I). In a previous paper a summary was presented of 241 operations on children with acyanotic lesions.[1] The purpose of the present paper is to present a report of the 193 operations performed on children with cyanotic lesions.

VALVULAR PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM

Valvular pulmonary stenosis with intact ventricular septum is not associated with cyanosis except in the presence of a patent foramen ovale or atrial septal defect. The pulmonary flow is equal to the systemic flow as long as the right ventricle by increased work and rise in pressure can provide an adequate output against the resistance of the stenotic pulmonary valve. When the rise in right ventricular pressure becomes sufficiently great to produce a retrograde increase in the pressure within the right atrium, unsaturated blood is shunted from the right into the left atrium through the interatrial communication, and pulmonary flow is diminished. Valvotomy is indicated in all cases in which cyanosis is present.

There are useful guides to the differential diagnosis of an anoxic cyanotic infant with valvular pulmonary stenosis and intact ventricular septum, for whom valvotomy is essential, as distinguished from the infant with extreme pulmonary stenosis and ventricular septal defect, in whom a shunt operation must be used. The cyanotic infant with intact septum, in our experience, has presented a prominent systolic murmur in the pulmonary area associated with marked enlargement of the right atrium and right ventricle, with a tendency toward a globular contour of the heart. Because of the large hypertensive right atrium, the P waves in Lead II of the electrocardiogram become extremely high and peaked. Depression of the S-T interval and inversion of T waves in Leads II, III, and aV_F may be associated (Fig. 1). In the infant with extreme pulmonary stenosis and ventricular septal defect, one may frequently hear no murmur or only a soft

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The anesthesia was administered by Dr. Margery Van N. Deming and her staff prior to September, 1955, and subsequently was administered by Dr. Leonard Bachman and his staff.

systolic blow to the left of the sternum. The cardiac shadow may be small or only moderately enlarged and tends to show the typical boot-shaped contour. Although the P waves in the electrocardiogram may be peaked, they never attain the height characteristically seen in the infant with intact ventricular septum. T waves may be of low amplitude, but inversion of T waves associated with marked depression of the S-T segment has not been noted by us.

Pressure tracings taken from the right ventricle during cardiac catheterization show differential features.[2] Curves from a ventricle which has no adequate outlet, as in the case of severe pulmonary stenosis and intact ventricular septum, have a peaked symmetrical appearance, whereas, in the presence of a ventricular septal

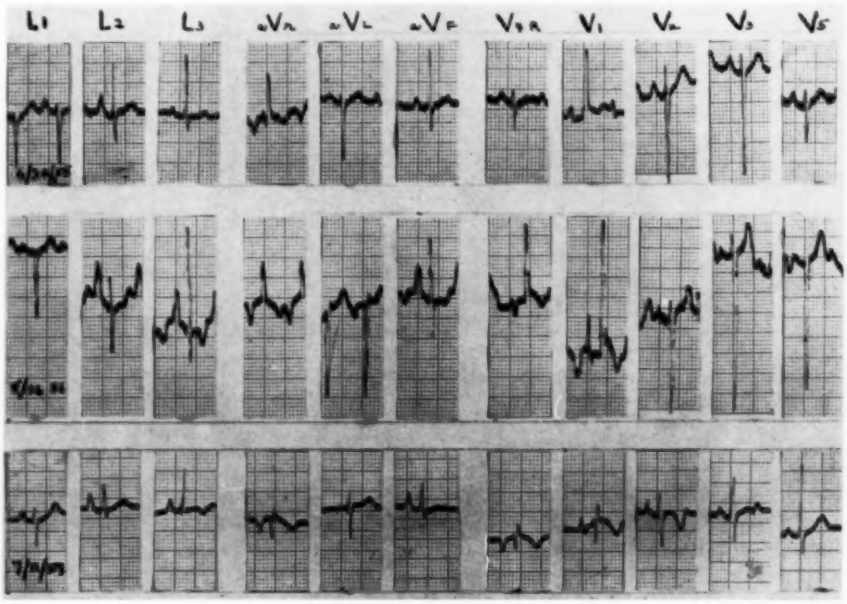
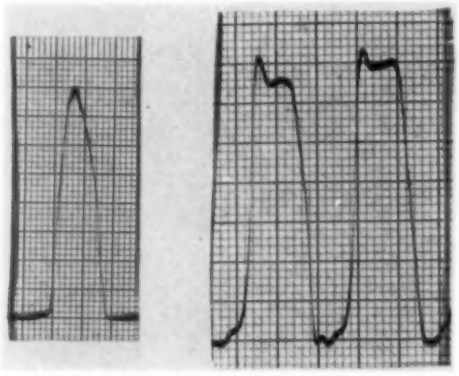


Fig. 1.—Serial electrocardiograms from an infant with valvular pulmonary stenosis and intact ventricular septum. Pulmonary valvotomy performed Sept. 5, 1956. Note the peaked P waves of high amplitude in Leads II, III, aV_F, and V_1, together with inversion of T^2 and T^3 in the tracing of Aug. 16, 1956, taken shortly before operation when the infant was intensely cyanotic and dyspneic. Also note the changing amplitude of the R wave in V_1, which reflects the changing degree of pressure within the right ventricle.

TABLE I. MORTALITY IN 434 CARDIOVASCULAR OPERATIONS

	NUMBER OF OPERATIONS	DEATHS	
		NUMBER	PER CENT
Acyanotic	241	6	2.5
Operable cyanotic	164	19	11.6
Transposed great vessels	17	10	58.8
Miscellaneous cyanotic	12	10	83.3
Total	434	45	10.4

defect the curves resemble those obtained from a ventricle with normal valvular outlet. They are asymmetric with a rapid ascent and plateau top (Fig. 2).



A. *B.*

Fig. 2.—Pressure curves from the right ventricle obtained at time of catheterization. *A*, Peaked symmetrical curve from a case of valvular pulmonary stenosis and intact ventricular septum. *B*, Asymmetric curve with rapid ascent and plateau top from a case of pulmonary stenosis and ventricular septal defect (tetralogy of Fallot).

Eleven operations were performed on children with valvular pulmonary stenosis and intact ventricular septum, with one death. The age range was 3 months to 13 years. All were cyanotic except a 13-year-old boy mentioned in the previous paper.[1] Five infants were so extremely anoxic and critically ill that cardiac catheterization did not seem warranted prior to operation. The diagnosis was confirmed in the operating room with an electromanometer. The single death was in a 3-month-old infant who went into ventricular fibrillation before the pericardium was opened. Valvotomy was performed immediately, but it was impossible to restore the normal heartbeat. A transventricular approach was used in all but one instance, in which case the valve was opened under direct vision through an incision in the pulmonary artery by the use of hypothermia. When the operation was done from below on small infants, the Potts knife alone was used. When the children were somewhat larger, the guillotine knife was utilized in addition, in order to be certain of getting a wide opening. In a few instances in which the guillotine knife was used, the right ventricular pressure was reduced to normal immediately. There was considerable drop in the right ventricular pressure in all cases. In those in whom the pressure remained above normal at the close of operation, further decrease of pressure occurred with the advance of time, as evidenced by the return of the electrocardiogram to normal (Fig. 1).

TETRALOGY OF FALLOT (PULMONARY STENOSIS AND VENTRICULAR SEPTAL DEFECT)

In the majority of instances the diagnosis of tetralogy of Fallot was made on a clinical basis. Special

studies such as angiocardiography and cardiac catheterization were used only in exceptional cases. Except for one recent operation, which was carried out successfully under direct vision with the aid of cardiopulmonary bypass, and two Brock procedures with unfavorable outcomes, all patients were operated upon with the hope of producing some type of left-to-right shunt (Table II). One hundred and thirty-two operations were carried out on 129 patients with a shunt procedure in mind, and it was possible to do an anastomosis in 123 instances (Fig. 3). We have included in this group patients with pulmonary atresia and ventricular septal defect (pseudotruncus arteriosus) as well as classic cases of tetralogy of Fallot. Operation has not been refused to any child either because of the severity of his condition or because the presence of a pulmonary artery could not be detected on the roentgenograms, since it has been our experience that even

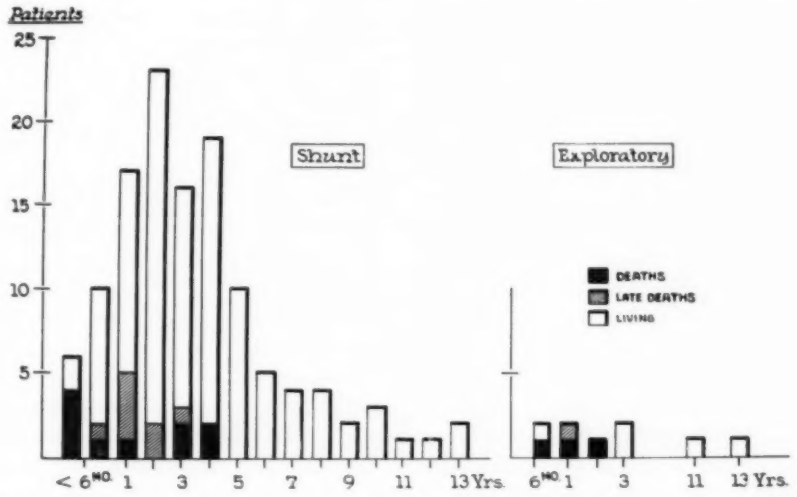


Fig. 3.—One hundred and thirty-two operations on individuals with pulmonary stenosis and ventricular septal defect (including pseudotruncus arteriosus and tetralogy of Fallot). Total operative death rate 9.9 per cent: 123 shunt procedures with 10 deaths within 30 days and 8 late deaths: 2 within 8 months; and 9 exploratory operations with 3 deaths within 30 days and one death 8 months after operation.

TABLE II. TETRALOGY OF FALLOT*

	NUMBER OF OPERATIONS	DEATHS		LATE DEATHS	
		NUMBER	PER CENT	NUMBER	PER CENT
Anastomosis					
6 weeks to 3 years old	56	6	10.8	7	12.5
3 years to 13 years old	67	4	5.9	1	1.5
Exploratory	9	3	33.1	1	11.1
Brock procedure	2	2	100.0	—	—
Pleurectomy	2	0	0.0	—	—
Open heart	1	0	0.0	—	—
Total	137	15	10.9	9	6.5

*Includes cases of pseudotruncus arteriosus.

when pulmonary atresia exists, it may still be possible to find a pulmonary branch suitable for anastomosis.

We have preferred a shunt procedure rather than direct attack upon the stenotic lesion through a transventricular approach, since we felt that it was not wise to relieve the pulmonary stenosis unless the ventricular septum could be closed at the same time. Our policy within recent years has been to defer operation on children with pulmonary stenosis and ventricular septal defect unless they were severely handicapped, with the thought of performing a completely corrective procedure at a later date, utilizing cardiopulmonary bypass. In small moribund infants, an aortic pulmonary anastomosis has been the procedure of choice. For about three years preceding 1950, an aortic-pulmonary anastomosis was carried out routinely on children with tetralogy of Fallot regardless of age. Since a number of these children seemed to develop undue cardiac enlargement, we have returned to the use of subclavian-pulmonary artery anastomosis on children who weigh as much as 10 kilograms or more.

In 9 patients no anastomosis was created. In January, 1948, the chest was closed in a 13-year-old boy because of a pressure reading of 45 cm. of water in the pulmonary artery, with the thought that this was too high a pressure to warrant the creation of an anastomosis. Subsequently, shunt procedures were performed with good results on several children with pulmonary pressure of this degree. In 1953, no definitive procedure was attempted on an 11-year-old girl who developed peripheral shock when the chest incision was made. Perhaps because of resultant adhesions, she has improved following thoracotomy alone. In five children no pulmonary artery could be located. Three died shortly after operation and one died during an anoxic attack seven months later. In the fifth child it was possible one year later to create a subclavian-pulmonary artery anastomosis in the opposite side of the chest which has functioned successfully for eight years. In another child, in whom no subclavian artery was found, it was also possible to perform a Blalock procedure on the opposite side one year later.

In 1949, the position of the aortic arch was diagnosed incorrectly in a 9-month-old infant in whom an aortic-pulmonary anastomosis was produced successfully in the opposite chest three weeks later. This error led to the study of the contour and position of the trachea and bronchi as a guide to the position of the aortic arch.[3] With good roentgenologic technique, moreover, it is possible, in the majority of cases, to see the shadow of the descending aorta even in young infants. Visualization of the esophagus with barium is now used only as a guide to the presence of anomalous vessels or enlargement of the left atrium.

The age range in the total group of children was from 6 weeks to 13 years. The death rate was extremely high in the first year of life since 6 deaths followed 18 operations, including those in whom no anastomosis could be made. However, infants of this age were referred for operation only when it became evident that they

could not live, and grow, out of oxygen. Those who died showed extreme hypoplasia of the infundibulum and pulmonary arteries, with extreme pulmonary stenosis or atresia. In the second year of life, there were 2 immediate deaths (10.5 per cent) and 2 deaths within 8 months in 19 operations. The only death in 24 children aged 2 years was in a girl with pulmonary atresia in whom an exploratory operation was done. The death rate in 37 children under the age of 2 years was 21.6 per cent. Five deaths (5.3 per cent) occurred in 95 children 2 years of age or over. There were no deaths in 34 operations on children over the age of 4 years, including 2 exploratory operations. In the entire series of 132 operations, there were 13 deaths (9.9 per cent) within the first 30 postoperative days, and 9 late deaths (6.8 per cent).

In 123 children in whom an anastomosis was created there were 10 deaths (8.1 per cent): 6 deaths (10.8 per cent) in 56 children under 3 years, and 4 deaths (5.9 per cent) in 67 children aged 3 or more.

Of the 9 late deaths in the entire group, 3 occurred within 8 months after discharge, all in infants operated on within the second year of life. In 1 it was impossible to create an anastomosis. In the other 2 there was evidence that the anastomosis was not functioning. Death occurred subsequently in 6 children: 13 months after operation in an infant whose anastomosis was not functioning; 18 months after operation in a Mongol with congestive failure; and 2½ years after operation in a Mongol who died of acute tracheobronchitis. The seventh and eighth deaths occurred 3 and 8 years postoperatively as a result of brain abscess. The ninth child improved markedly immediately after operation but, again, became cyanotic and dyspneic, and died 4 years later at another institution following infundibulectomy.

In 3 additional survivors the anastomosis has failed to function. Four children are also becoming increasingly cyanotic following a period during which they had manifested excellent improvement.

One child whose anastomosis failed to function was admitted in November, 1948, at which time a shunt was made between the left pulmonary artery and descending aorta. Exploration of the pericardial sac disclosed no main pulmonary artery. Although cardiac arrest occurred for 6 minutes, she recovered from the operation but showed no improvement. She remained extremely dyspneic with frequent anoxic episodes until April, 1950, when a right thoracotomy was performed. The parietal pleura was resected, and powdered asbestos was sprinkled into the chest to favor the formation of adhesions whose blood vessels might penetrate the lung and the chest wall.[4] She improved remarkably following this procedure, which was repeated in the left side of the chest in May, 1952. At present, although cyanotic and moderately restricted in exercise tolerance, she is an attractive mentally alert 13-year-old girl who attends school and leads a relatively normal life.

Fifteen per cent of 123 children with tetralogy of Fallot who have undergone a shunt operation have died either immediately or in subsequent years. An additional 5 per cent

remain, or have become, dyspneic and cyanotic following operation. The remaining 80 per cent lead a normal existence in varying degrees, ranging from individuals who can indulge in all activities to frail children who are able to attend school but who tire easily. These frail children are usually young, and as time goes on they often gain stamina and improve in nutrition. This is a remarkable result since all of these children were greatly handicapped at the time of operation and destined for early death. The present series is small and, in part, has been followed for only a short period of time. A follow-up study from Baltimore showed that 67 per cent of 244 patients who survived a shunt operation and were benefited by it had maintained their improvement 5 to 8 years after operation.[5] In the first 100 children on whom a shunt procedure was performed in Chicago, results 6 to 8 years after operation were good in 68 per cent and fair in 16 per cent.[6]

It is readily admitted that a shunt procedure is palliative rather than curative. The hazard of possible brain abscess faces all individuals with ventricular septal defect and a right-to-left shunt. Approximately one quarter of our group of survivors either have marked cardiomegaly or are beginning to show undue vascularity of the lung fields. In a few the pulmonary artery on the side of the operation has dilated to aneurysmal proportions. It is obviously desirable to operate upon these children by the direct approach, using cardiopulmonary bypass, in the hope of converting a complicated defect into a more nearly normal heart. Whether this can be carried out in small, extremely anoxic infants is questionable. Moreover, the death rate in the shunt operations in older children is very low. There were no deaths in children 4 years of age or over in our present series. Nevertheless, the idea of providing complete correction of the cardiac defect is most appealing, and now that cardiopulmonary bypass is available, this procedure will be carried out in many individuals. Time alone will give us the long-term results of the incision in the myocardium. It is obvious that concern over the fate of the prosthesis which may be necessary for the closure of the ventricular septal defect or for enlargement of the outflow tract of the right ventricle can be abolished only after many years of observation.

TRICUSPID ATRESIA WITH INADEQUATE PULMONARY CIRCULATION

The diagnosis of tricuspid atresia with inadequate pulmonary circulation was made on 11 cyanotic children with roentgenographic evidence of diminished pulmonary vasculature and an electrocardiogram with a QRS pattern of left ventricular hypertrophy. The diagnosis was verified preoperatively in one 4-year-old girl with angiocardiography, by means of which it was possible to see the contrast media pass directly from the right atrium into the left atrium and left ventricle. A triangular area near the diaphragm in the region of the right ventricle remained unfilled (Fig. 4). The diagnosis was confirmed at autopsy in 2 children who died following operation.

The age range was 2 months to 4 years. Three children were less than 1 year of age and 4 were in the second

year of life. An aortic-pulmonary anastomosis was made in 7 children and a subclavian-pulmonary anastomosis in 4. In 2 of the latter children, an atrial septal defect was also created. The results of operation on the whole have been poor. Three infants under the age of 14 months developed right-sided congestive failure following an aortic-pulmonary anastomosis. In 2, death occurred 40 days and 3 months postoperatively. The third child led a fairly normal life for 6 years despite massive cardiomegaly, hepatomegaly, and splenomegaly. Death was due to a fulminating acute febrile illness. A 15-month-old boy died of congestive failure 2 weeks after a subclavian-pulmonary artery shunt was performed. A 2-year-old girl, in whom a right Blalock procedure had been performed and an atrial septal defect created, died of a staphylococcal pulmonary infection 7 weeks after operation. Necropsy revealed a patent anastomosis and an atrial septal defect 1.0 cm. in diameter. Of the 11 children operated upon for tricuspid atresia, 6 remain alive. The children who have survived show a greater degree of cyanosis and polycythemia than is usually seen after a shunt procedure in the child with pulmonary stenosis and ventricular septal defect.

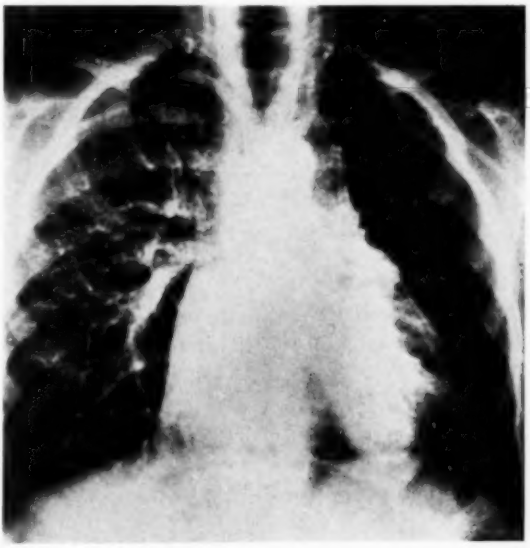


Fig. 4.—Tricuspid atresia. Angiocardiogram of a 4-year-old girl with marked cyanosis and left ventricular preponderance in electrocardiogram. Contrast medium visible in right atrium, left atrium, left ventricle, and large aorta. Triangular shadow near diaphragm in region of right ventricle remains unfilled. (From Ash, R.: Congenital Cardiovascular Abnormalities; in Diagnosis and Treatment of Cardiovascular Disease, edited by Stroud and Stroud, F. A. Davis Co., 1957, p. 111.)

The question has arisen as to whether the difference between success and failure in these patients is the size of the anastomosis made between the aorta and the left pulmonary artery, or whether the left-to-right shunt

increases the pressure in the left atrium sufficiently to close the patent foramen ovale, giving a poor result in those instances where an atrial septal defect of adequate size is not present. Examination of the hearts of two infants with right-sided congestive failure who died after operation certainly suggested that creation of an atrial septal defect might have been beneficial and that the foramen ovale may have been closed by an increase of pressure in the left atrium. In one of these infants a subclavian-pulmonary artery anastomosis had been created. In the child whose electrocardiogram shows high peaked P waves in Lead II, indicative of the presence of an enlarged right atrium under pressure, the patency of the foramen ovale may be too small to permit survival following a shunt procedure, unless an atrial septal defect is created.

It is possible that the procedure suggested by Glenn,[7] in which the superior vena cava is anastomosed to the right pulmonary artery, may be the optimum procedure in children with tricuspid atresia as well as in those with single ventricle and pulmonary stenosis.

TOTAL TRANSPOSITION OF PULMONARY VEINS

If all pulmonary veins empty into the right atrium, the foramen ovale must remain patent. The systemic circulation is supplied by mixed veno-arterial blood through the atrial septal defect. The left atrium and ventricle are hypoplastic. A high percentage of individuals with this lesion die in infancy of right-sided congestive failure.

The most common type of defect with total anomalous pulmonary venous drainage is that in which all pulmonary veins connect with a left common vertical vein which flows into the right atrium through the superior vena cava by way of the left innominate vein. This may be recognized on the roentgenogram of the chest by the figure-of-8 contour of the cardiac shadow (Fig. 5).

A limiting factor in correction of this lesion would seem to be the size of the anastomosis, which must be sufficiently large to permit free flow of blood from the lungs. It has been pointed out that the waist of the atrial appendage is usually smaller than the common pulmonary vein.[8] Anastomosis must therefore be made to the body of the left atrium. The heart of the individual with total transposition of the pulmonary veins tolerates manipulation poorly. Cardiopulmonary bypass would seem essential in order to permit the creation of an anastomosis of sufficient size and in the proper location to function adequately.

There were five children with a left common vertical vein in our series. Mention has been made in a previous paper of the critically ill 2-month-old infant with such a lesion who was operated on because of a continuous murmur heard below the left clavicle and who died one week following simple exploration. An operation was performed on the remaining four children under hypothermia before our cardiopulmonary bypass machine was available in the hope of performing an anastomosis between the left atrial appendage and the left common vertical vein. In two of these patients, a 6-year-old boy and a 7-year-old girl,

the anastomosis was accomplished successfully. The 7-year-old girl was the only one who was not in serious condition at the time of operation, so that it was possible to take pressure readings. As a result, it was obvious that the pulmonary venous pressure would increase unduly if the left vertical vein were completely occluded. An anastomosis 1.5 cm. long was made. However, when the vertical vein was occluded tentatively, pulmonary venous pressure rose from 12 to 37 cm. of water, while the pressure in the left atrium remained at 7 cm. of water. A second anastomosis was made, 0.8 cm. in length. Following this, clamping of the vertical vein produced a pressure of 30 cm. of water. It was felt that the anastomoses were not sufficiently large to prevent increased pressure in the pulmonary veins if the vertical vein was ligated completely. The lumen was constricted about 60 per cent by a ligature. In the operation on the 6-year-old boy, the vertical vein also was not ligated completely. Although both patients have improved as a result of this shunt, part of the blood returning from the lungs still enters the right atrium through the constricted vertical vein. In the other two children, one a 2-month-old infant and one a 3-year-old boy, ventricular fibrillation occurred during the period of anastomosis. In spite of cardiac massage and other resuscitative efforts, the boy could never be revived and the infant died 8 hours postoperatively.

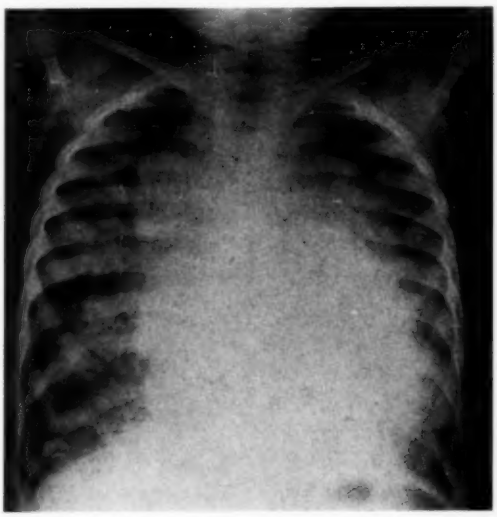


Fig. 5.—Complete anomalous venous drainage into the right atrium through a left common vertical vein. Note widening of superior mediastinal shadow due to dilated superior vena cava on right, and common vertical vein on left. The superior mediastinal shadow and the cardiac shadow form the contour of a figure 8. (From Ash, R.: Congenital Cardiovascular Abnormalities; in Diagnosis and Treatment of Cardiovascular Disease, edited by Stroud and Stroud. F. A. Davis Co., 1957, p. 131.)

Recently, complete correction of this lesion under direct vision utilizing

cardiopulmonary bypass has been reported. A large anastomosis was made between the left atrium and the anomalous pulmonary venous channel situated posteriorly, after which the atrial septal defect was closed and the vertical vein ligated.[9]

The remaining child with total anomalous pulmonary venous connection was actually the first child operated upon, and she had an entirely different type of defect. She was a 13-month-old infant who had been arrhythmic and in congestive failure for months. A right thoracotomy was performed in February, 1954, under hypothermia, with the thought that a simple atrial septal defect was present. The right superior pulmonary vein entered the superior vena cava and the right inferior pulmonary vein disappeared below the diaphragm. No definitive procedure was attempted. One month later, however, a left thoracotomy was performed. At that time, the left superior and inferior pulmonary veins were found to form a common vessel which disappeared below the diaphragm. An anastomosis was made between the left superior pulmonary vein and the left atrial appendage through an incision 1.5 cm. in length. The common vein coursing toward the diaphragm was then ligated so that the blood from the entire left lung was forced to flow into the left atrium. The infant suffered pulmonary edema for several hours, but subsequently made a complete recovery. At present, all blood from the right lung still enters the right atrium through the vena cava, but the heart has decreased in size and there has been no arrhythmia or congestive failure since the operative procedure.

COMPLETE TRANSPOSITION OF THE AORTA AND PULMONARY ARTERY

In the presence of complete transposition of the great vessels, two independent circulations exist, the aorta transporting venous blood from the right ventricle to the body and the pulmonary artery sending arterial blood from the left ventricle to the lung. Life can be maintained only if one or more associated defects permit oxygenated blood to reach the systemic circulation. In most cases the diagnosis can be made by an evaluation of the clinical picture and the roentgenogram of the chest. Children with complete transposition of the great vessels tend to have a large head and barrel chest. They may develop dyspnea and hepatomegaly without being subject to anoxic attacks. Severe anoxia is most likely to occur in the infant with small or no septal defects when the ductus is closing. Roentgenograms of the chest show generalized cardiac enlargement with an oblique downward curve of the left border. The superior mediastinal shadow is shortened and frequently narrow. The pulmonary vascular shadows are increased in the majority of cases. The minority with pulmonary stenosis are difficult to distinguish from individuals with tetralogy of Fallot except by an angiocardiogram.

The majority of babies with transposition of the great vessels fail to survive the first year. Any useful operation must be applicable during the first weeks or months of life. In a few instances surgeons have succeeded in completing retransposition of the great vessels and coronary arteries, but no infant has lived more

than a few hours or days. Children with transposition of the great vessels, who also have pulmonary stenosis, will benefit from a shunt procedure and creation of an atrial septal defect.

In the present series an atrial septal defect has been created in 10 infants with transposed great vessels and excessive pulmonary circulation in order to assure better mixing of blood within the heart. Four are still alive. The oldest, who was operated on 6 years ago, is a very intelligent boy who does well at school, although he cannot engage in active exercise. Two boys lead active lives 4 years after operation. The youngest child, who has survived 2 years, is delayed in growth and development. All still show cyanosis and polycythemia, but to a lesser degree than was noted preoperatively.

Transposition of the superior vena cava and right superior pulmonary vein was performed in a 3-month-old infant who showed great improvement for several months, after which she developed increasing pulmonary edema and died 5 months postoperatively. At necropsy, the anastomoses were patent but the valve of the foramen ovale was closed, presumably due to high pressure in the left atrium. It is possible that this infant might have continued to do well if an atrial septal defect had been created.

Anastomosis of the right pulmonary veins to the right atrium was performed in a 6-month-old infant with immediate improvement, but sudden death occurred several months later in association with a mild infection. All of the operations referred to above were performed on deeply cyanotic and critically ill infants ranging from 4 weeks to 18 months in age. Only two had reached their first birthday.

Anastomosis of the right pulmonary vein to the right atrium was performed in a 5-year-old boy who died of pulmonary hemorrhage 14 hours after operation. His temperature had been allowed to drift to 22.5° C. at the time of the operation.

Baffes[10] has obtained favorable results by anastomosis of the inferior vena cava to the left atrium with the interposition of an aortic graft, followed by anastomosis of the right pulmonary veins to the right atrium. It would seem doubtful whether a graft inserted in a young infant would continue to function adequately with the growth of the child. This procedure has been carried out only once in this series, on a 7-year-old boy. He showed great improvement for 36 hours, but suddenly developed heart block and failed to respond to resuscitative procedures. At necropsy, all anastomoses were open and there was a large ventricular septal defect. The intrapulmonary arterioles showed intimal proliferation with superimposed thrombi.

Of the 17 patients operated upon for total transposition of the aorta and pulmonary arteries, only 4 remain alive. All of these had an atrial septal defect created at the time of operation.

PULMONARY ARTERIOVENOUS FISTULA

A right lower lobectomy was performed because of the presence of a pulmonary arteriovenous fistula in a very cyanotic girl, whose cyanosis disappeared immediately after removal of the pulmonary tissue (Fig. 6).

MISCELLANEOUS CONDITIONS

There were 12 children with incorrectly or incompletely diagnosed lesions for which no suitable operation was available at the time of surgery. They were critically ill children, referred in a desperate hope that an operable lesion might be found. Included in this group were three small infants with pulmonary atresia upon whom a shunt operation was performed but who, at necropsy, were found also to have a common atrioventricular canal. Two had asplenism and at present would have been eliminated as candidates for surgery by evaluation of the hemogram. Also included are an infant with truncus arteriosus and one with total transposition of the pulmonary veins who were explored for the possible presence of a patent ductus. A cyanotic

Fig. 6.—Pulmonary arteriovenous fistula. Angiocardiogram, taken one second after injection of contrast medium, shows opacification of right atrium, right ventricle, pulmonary artery, and dilated vascular spaces in lower right lung. From a 3-year-old girl whose marked cyanosis disappeared after right lower lobectomy. (From Ash, R.: Congenital Cardiovascular Abnormalities; in Diagnosis and Treatment of Cardiovascular Disease, edited by Stroud and Stroud, F. A. Davis Co., 1957, p. 135.)

TABLE III. OPERABLE CYANOTIC LESIONS

	NUMBER OF OPERATIONS	DEATHS		LATE DEATHS	
		NUMBER	PER CENT	NUMBER	PER CENT
Tetralogy of Fallot	137	15	10.9	9	6.5
Tricuspid atresia	11	1	9.1	4	36.4
Pulmonary stenosis, intact ventricular septum	10	1	10.0	0	0
Total transposition of pulmonary veins	5	2	40.0	0	0
Pulmonary arteriovenous fistula	1	0	0.0	—	—
Total	164	19	11.6	13	7.9

infant with Ebstein's deformity of the tricuspid valve was suspected of having pulmonary stenosis, as was a 15-year-old girl with reverse ductus and a pulmonary artery overriding a ventricular septal defect.

In 164 operations on cyanotic children with potentially operable lesions, there were 19 deaths (11.6 per cent) and 12 late deaths (7.9 per cent) (Table III). In 29 operations on cyanotic children with inoperable lesions (including complete transposition of the great vessels), there were 20 deaths.

SUMMARY

A review has been presented of 193 cardiovascular operations on cyanotic children. The mortality was 20 per cent. In 164 operations on cyanotic children with potentially operable lesions, there were 19 deaths (11.6 per cent).

There were 10 operations on cyanotic children with valvular pulmonary stenosis and intact ventricular septum, with one death. Excellent clinical results have been obtained in the survivors.

A shunt procedure was used in all but 3 of the 126 patients in whom a definitive operation was performed for tetralogy of Fallot. The operative mortality was 8 per cent and the late deaths constituted 7 per cent. Eighty per cent have obtained a good clinical result. Time alone will tell whether correction of this lesion under direct vision will improve these results.

A shunt procedure was performed on 11 children with tricuspid atresia. In two an atrial defect was also created. There was one operative death and 4 late deaths. The survivors show a greater degree of cyanosis than is usually seen in the child with tetralogy of Fallot.

Only 4 of 17 infants remain alive after various operations for correction of transposition of the aorta and pulmonary artery. An atrial septal defect was created in each of these survivors.

Our experience would indicate that it is difficult, or impossible, to correct total transposition of the pulmonary veins fully without cardiopulmonary bypass, although considerable improvement was obtained in 3 of 5 patients on whom a pulmonary vein was anastomosed to the left atrial appendage under hypothermia.

A right lower lobectomy was performed on a very cyanotic girl with pulmonary arteriovenous fistula, resulting in immediate disappearance of cyanosis.

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Lo the Placebo

Dr. W. T. Gairdner discussing the relation of the medical man to society at large: ". . . it is impossible that the physician should be a mystery-man, enshrouding himself in the arcana of his science: the public are beginning to know too much." He describes the hysterical lady who deciphers her doctor's prescription allowing him no recourse but to ". . . ransack the stores of the chemist for the last organic compound with a name of six syllables, or to operate with metals more unfamiliar than even cerium, and titanium, and palladium." Any who have met with such a patient must have found her "like an old bird, not to be caught with chaff."

From a review of "On Medicine and Medical Education: Three Lectures," by W. T. Gairdner, M.D., Fellow of Royal College of Physicians and Lecturer on Physic, Edinburgh, 1858, in BRITISH MEDICAL JOURNAL, January 8, 1859.

GALACTOSEMIA PRESENTING WITH GANGRENE

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GALACTOSEMIA has been recognized since 1908.[1] It has recently been shown to result from a deficit in the transferase enzyme in the reaction[2]: galactose-1-phosphate + UDP glucose *(gal-1-PO4 uridyl transferase)* glucose-1-phosphate + UDP galactose. The accumulation of galactose-1-P resulting from the metabolic block is thought to have a toxic effect on such tissues as liver, brain, and crystalline lens. The disease often presents, during the first few weeks of life, with jaundice, hepatomegaly, failure to gain, and ascites; it is often complicated by sepsis. The present case is reported because of an unusual associated finding, gangrene of the extremities.

CASE REPORT

The patient, a white girl, was born at 39 weeks' gestation by cesarean section because of cephalopelvic disproportion. Pregnancy was uneventful, the membranes were intact, and the mother was not in labor. Birth weight was 6 pounds, 11 ounces. She was considered normal, but fed poorly in the hospital and was discharged after 7 days, weighing 6 pounds. The parents were healthy young adults and there was no history of consanguinity. One older sibling, a girl, is living and well.

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At home she was given an evaporated milk formula, but sucked weakly, requiring an hour or more to take 1½ oz. At 10 days of age she was considered a feeding problem by her pediatrician and the formula was changed to Similac without beneficial effect.

At 16 days of age she developed a mild diarrhea with watery, yellow stools, which continued for 2 days. She was then admitted to St. Joseph's Hospital of Orange County for mild dehydration, weighing 6 pounds, 3 ounces. The abdomen was described as distended. Hemoglobin concentration was 13 Gm. per cent. The white blood count was 27,000, with 52 segmented neutrophils, 10 per cent band neutrophils, 22 per cent lymphocytes, 13 per cent monocytes, and 3 per cent eosinophils. The urine contained protein 2+ and reducing substance 1+. An Alacta formula was prescribed, and the next day her stools were more formed. On the second hospital day a low-grade fever was noted, and parenteral penicillin and streptomycin were begun. On the third hospital day ascending cyanosis of the feet was noted, closely followed by gangrene. Twenty-fours after the onset of gangrene she was transferred to the Childrens Hospital.

Physical Examination.—Temperature was 36° C., pulse 160, and respirations were 25 per minute. The head circumference was 33 cm., the crown—rump measured 31 cm., and length 44 cm. Her weight was 6 pounds, 7 ounces. She was slightly undernourished and lethargic without evidence of dehydration. The abdomen was markedly distended,

Fig. 1.

Fig. 2.

Fig. 1.—The patient at the age of 3 weeks, on admission.

Fig. 2.—The patient's feet on admission.

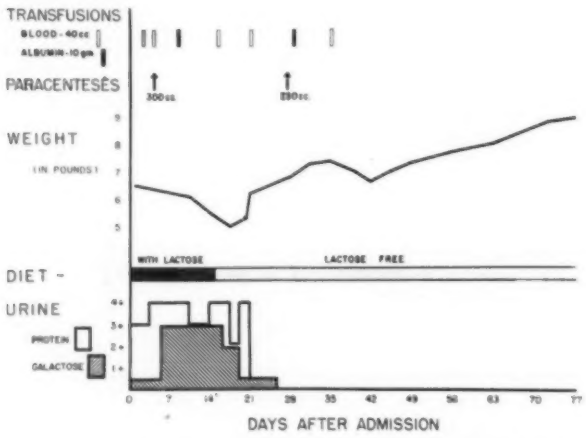

Fig. 3.—The patient's course in the hospital.

with reddish-blue discoloration of the skin and a prominent superficial venous pattern. There was an ecchymosis 2 by 3 cm. in diameter adjacent to the umbilicus. The liver was palpable 4 cm. below the right costal margin. Bowel sounds were hypoactive. There was pitting edema of the labial folds and both legs. Femoral pulses were palpable, and prompt capillary return occurred after blanching from pressure on both heels. The skin of both legs was of normal color and temperature to the ankles. The feet were discolored a ruddy bluish-red. The skin of the distal half of the right foot was black, dry, and cool, with the exception of the fifth toe and lateral aspect of the fourth toe. The left foot showed the same black, dry skin on the entire second toe, extending over the dorsum of the foot for 2 cm. (Figs. 1 and 2).

Course in Hospital (Fig. 3).—Initial working diagnoses were sepsis with pedal gangrene and mesenteric and/or high inferior vena caval thrombosis. Hemoglobin concentration was 12.5 Gm. per cent, and the white blood count 44,000. Urinalysis the next day revealed protein 4+ and no reducing substance. The carbon dioxide content of the serum was 9 mEq. per liter. X-rays of the abdomen suggested free intraperitoneal fluid. Blood cultures were sterile, culture of the nasopharynx yielded *Micrococcus pyogenes* var. *aureus*, and no pathogenic organisms were recovered from cultures of stools.

Appropriate fluids were given parenterally. Chloramphenicol and oleandomycin were administered intravenously. The feet were washed with Phisohex and covered with dry sterile dressings.

The next day two normal stools were passed, and a dilute formula containing Dryco was offered. On the third hospital day mild generalized pitting edema was observed, and the sodium and water were reduced in fluids administered parenterally. On the fourth day a diagnostic paracentesis yielded 300 c.c. clear yellow fluid (specific gravity 1.014, protein 322 mg. per cent, culture sterile). Generalized edema disappeared in two days, but ascites and edema of both legs persisted. On the ninth

Fig. 4.—The patient during the fifth week in the hospital.

hospital day the serum albumin was 2.3 Gm. per cent, and salt-poor albumin administered intravenously raised the concentration of serum albumin to 4.4 Gm. per cent. A diet low in salt and high in protein (Lonolac and Casec mixture) was given in an effort to retard the formation of ascites.[3]

Proteinuria and glycosuria had been demonstrated consistently. On the fourteenth hospital day the urinary

reducing substance was identified as galactose by paper chromatography. Blood sugar that day measured 227 mg. per cent (total reducing substance). Galactosemia was strongly suspected, and the formula was changed to Nutramigen (lactose-free). The serum albumin had declined to 2.7 Gm. per cent. Salt-poor albumin was given intravenously, restoring it to 4.5 Gm. per cent. From the thirty-fourth to the thirty-eighth hospital day, mild generalized pitting edema recurred, and then spontaneously disappeared. Edema of the legs and ascites, which had persisted since admission, disappeared concurrently.

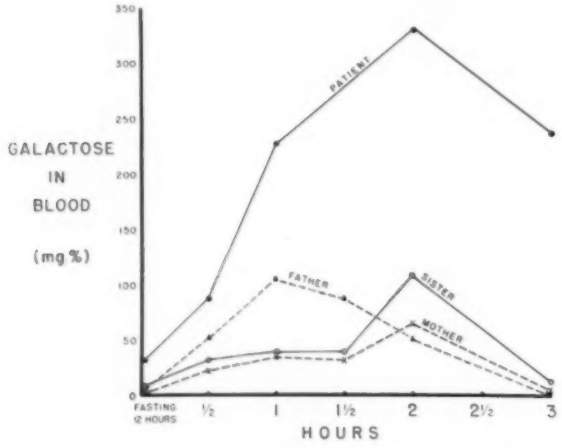

Fig. 5.—Galactose tolerance test of the patient and family.

From the fourteenth to the seventeenth hospital day, 6 to 7 loose yellow stools occurred daily. She accepted feedings poorly and became progressively dehydrated and tachypneic. Gastroenteritis induced by antibiotics was considered the most likely cause of the diarrhea. Blood cultures were sterile, and stool cultures failed to demonstrate pathogenic bacteria. The carbon dioxide content of the serum was less than 5 mEq. per liter. Discontinuance of broad-spectrum antibiotics and the parenteral administration of appropriate fluids to correct dehydration and acidosis resulted in marked improvement during the next few days.

During the first 3 weeks, 4 small blood transfusions were required to maintain the hemoglobin concentration above 10 Gm. per cent.

On the twenty-fifth hospital day abdominal distention recurred. Paracentesis yielded 250 c.c. clear yellow fluid (protein 1,638 mg. per cent, culture sterile). The serum albumin had declined to 2.7 Gm. per cent. Salt-poor albumin was given intravenously, restoring it to 4.5 Gm. per cent. From the thirty-fourth to the thirty-eighth hospital day, mild generalized pitting edema recurred, and then spontaneously disappeared. Edema of the legs and ascites, which had persisted since admission, disappeared concurrently.

On the thirty-second hospital day a mild cystitis due to *Escherichia coli* was treated with nitrofurantoin.

Gangrene of the feet did not progress after admission. During the first three weeks, the left foot and all but the first two toes of the right foot healed completely. By the fortieth hospital day, the second right toe had healed completely and only the distal phalanx of the first toe remained black, dry, and shrunken (Fig. 4).

During the last month in the hospital, she gained weight well, hepatomegaly decreased, and the small remaining area of gangrene became well demarcated. At the time of discharge on the seventy-seventh hospital day she weighed 8 pounds, 13 ounces. An oral galactose tolerance test was done three days prior to discharge when the patient was in excellent health.

The inability of this infant to handle a load of galactose is depicted in Fig. 5.

At the age of 6 months the distal phalanx of the first toe sloughed spontaneously. On examination at 9 months of age she had developed normally, and weighed 17 pounds.

DISCUSSION

Galactosemia presenting with gangrene is rare. Review of the literature reveals one other such case. Newman[4] described an 11-week-old infant with gangrene of the sole of one foot. Galactosemia was documented by galactosuria, and blood galactose of 220 mg. per cent. Treatment of the galactosemia resulted in general improvement, concomitant with healing of the gangrene. Etiology of the gangrene remains obscure. Another case reported by Lawrence and McCance[5] describes an 18-day-old infant with 4 areas of gangrene associated with glycosuria and hyperglycemia. This child finally improved on a formula containing added lactose, and probably did not have galactosemia.

The differential diagnosis of neonatal gangrene is adequately discussed in the literature.[6, 9, 10, 15, 16] Sepsis associated with multiple small venous and capillary thromboses may have contributed to the occurrence of gangrene in the present case despite failure to isolate an infectious organism from the blood. The severity of illness, fever, leukocytosis, and dehydration suggested systemic infection.

Arterial embolism and thrombosis have been known to cause gangrene.[6] Femoral arterial thrombosis was unlikely in this case because of the bilateral involvement, good femoral pulses, and normal color and temperature of the legs down to the ankles. Multiple small emboli with thromboses of arterial branches in the feet could not definitely be ruled out.

Venous thromboses rarely cause gangrene.[15, 16] Vena caval thrombosis at the level of the hepatic vein[7, 8, 16] was suggested early in this case by the history of diarrhea and dehydration, hepatomegaly, ascites, edema of both legs, and prominent abdominal venous collaterals. The preservation of skin color and temperature down to the ankles and the history of cyanosis followed by ascending superficial gangrene are characteristic of gangrene resulting from venous stasis. The rapid clearing of these signs made the diagnosis of vena caval thrombosis unlikely.

Conservative management has been recommended[11] for gangrene in infancy, and appears justified in the present case. Anticoagulant therapy was considered, but not employed because of uncertainty in diagnosis and the difficulty of repeated venepunctures in an infant.

The differential diagnosis of ascites in early infancy should include galactosemia.[12, 13] The mechanism of its formation in this condition is unclear. Ascites is known to result from interference with the flow of blood to and from the liver, from decreased serum oncotic pressure, and from hormonal disorders causing salt and water retention.[14] Cirrhosis, known to occur early in galactosemia, hepatic congestion, and hypoproteinemia were present in this case, and were probably contributing factors. The contributions, if any, from aldosterone and antidiuretic hormone were not determined.

Delay in the diagnosis and treatment of galactosemia frequently occurs when it presents with severe infection. Early treatment often includes removal of milk from the diet, and the administration of supplemental fluids parenterally. On a galactose-free diet, glycosuria rapidly subsides. It is not until oral feedings containing lactose are resumed that glycosuria recurs, arousing suspicion and eventual identification of the reducing substance. Another pitfall lies in the newer methods for urinary glucose determinations. Currently available paper-strip tests are specific for glucose, while those tests employing the classical methods of copper reduction identify all reducing sugars. In suspected cases of galactosemia the combined use of copper-reducing tests with the glucose-specific test will differentiate between glucose and other reducing substances. Final and accurate identification by paper chromatography can then be made. Since all infants with galactosuria do not have galactosemia, the diagnosis must then be confirmed by more specific methods such as galactose-tolerance test or assay of the red blood cells for gal-1-PO4 uridyl transferase.[17]

SUMMARY

A patient with galactosemia presenting with bilateral pedal gangrene and ascites is presented. The cause of gangrene is obscure, but it may be presumed to be due to sepsis associated with multiple small venous and capillary thromboses.

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DUODENAL ULCER WITH INTESTINAL OBSTRUCTION IN A NEWBORN CHILD

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ALTHOUGH peptic ulcers may occur at any age, and have been observed in stillborn infants, intestinal obstruction secondary to a duodenal ulcer in the neonatal period is rare. In 1941, Bird, Limper, and Mayer[1] reviewed the literature on peptic ulcers of the stomach and duodenum in infants and children. They found only one case of obstruction resulting from a peptic ulcer in a child less than 14 days of age. This is the only such case reported in the English language literature.

CASE REPORT

A white boy was born by spontaneous delivery at William Beaumont Army Hospital after an uncomplicated pregnancy and labor to a 40-year-old mother. The mother was blood group A, Rh positive, and had a negative serologic reaction for lues. The infant's birth weight was 6 pounds, 11 ounces (3,060 grams). One hour and thirty-five minutes after birth a small amount of bright red blood was seen oozing from the baby's mouth, and it was noted that he was jaundiced. At 5 hours of age the infant appeared pale. At this time the hemoglobin was 19.1 Gm. and hematocrit 59 per cent. The infant was blood group A, Rh positive, and the direct Coombs test on the infant's blood was negative. Total serum bilirubin was 4.1 mg. per cent, indirect 0.2 mg., direct 3.9 mg. Bleeding and clotting times were normal. By 8 hours of age, the hemoglobin had dropped to 13.5 Gm. Two hours later the patient began to pass bright and dark red blood per rectum. This blood contained hemoglobin which was alkaline resistant. At 11 hours of age the baby was transfused with 50 ml. of whole blood. Esophagoscopy, done by the oto-largyngology service, revealed a normal esophagus.

The first feeding (an evaporated milk formula) was given at 13 hours of age. The infant began to vomit one hour later and continued to vomit frequently. The vomitus contained a few flecks of blood. At 24 hours of age he again passed two large bloody stools. Twelve hours later he was given an additional 30 ml. of whole blood. By 72 hours after birth, the vomiting became infrequent and was free of blood. On the next day the stools were grossly normal.

During the entire period of hospitalization, the abdomen remained soft, apparently nontender, and was never abnormally distended. The infant did not show any signs of respiratory or central nervous disease, and was discharged six days after delivery in good condition. His hemoglobin at the time of discharge was 17.5 Gm.

He was readmitted to the hospital at the age of 28 days with a history of having vomited after every feeding for the 10 days prior to admission. The vomitus was said to have been free of gross blood or bile. The stools, which had been normal in consistency and frequency, had also been

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free of gross blood. Physical examination on admission revealed an icteric infant in no distress who weighed 7 pounds, 3 ounces (3,260 grams). He was having projectile vomiting, and peristaltic waves, coursing from left to right on the anterior abdominal wall, were seen after feeding. No abnormal abdominal mass was felt. Roentgenograms of the abdomen were interpreted as showing signs of obstruction and revealed very little gas in the intestines. The stomach, visualized by barium given by nasogastric tube, did not empty completely in three hours, at which time only a small amount of the barium was seen in the jejunum. The complete blood count and bleeding and clotting times were normal. Reticulocyte count was 1.4 per cent, total serum bilirubin 9.45 mg. per cent, direct 0.31 mg., indirect 9.1 mg. Alkaline phosphatase was 6 Bodansky units. Gastric fluid obtained by lavage contained a small amount of blood. At 30 days of age an exploratory laparotomy was performed through an upper abdominal midline incision. The gall bladder was found to be adherent to the anterior portion of the duodenum, and cicatricial searring was present about the first part of the duodenum. On opening the stomach in the antral area, a bleeding ulcer was seen on the anterior wall of the duodenum. Edema and scar tissue in the wall of the duodenum had produced almost complete obstruction. The liver and extra hepatic biliary system appeared normal. An anterior gastrojejunostomy was performed. The infant received whole blood and intravenous fluids during the operation and withstood the procedure well.

The postoperative course was uneventful except for occasional episodes of vomiting. Lytren was given orally 24 hours after surgery. Within 48 hours feedings of skimmed milk were started. Two weeks after surgery roentgenographic study of the upper gastrointestinal tract showed that barium entered the jejunum through the gastrojejunostomy. Barium was also seen to enter a normal-appearing duodenal bulb. Three weeks later, at the time of discharge, the jaundice had completely cleared, the baby was symptom free and weighed 8 pounds, 1 ounce (3,650 grams). He was taking a diet of evaporated milk formula, strained meats, and cereal. At the age of 80 days the patient weighed 12 pounds, 1 ounce (5,500 grams). No vomiting had been noted since leaving the hospital. At this time roentgenograms of the upper gastrointestinal tract showed the gastrojejunostomy to be closed with all of the barium passing in a normal fashion through the duodenum, which was radiographically normal. At 12 months of age the infant weighed 24 pounds, 11 ounces (11.25 kilograms). He had not had any further gastrointestinal symptoms and was developing normally.

DISCUSSION

This patient was noted to have bleeding from the gastrointestinal tract and jaundice 95 minutes after delivery. The hemorrhage continued until 3 days of age and was severe enough to necessitate two transfusions. He was discharged from the hospital at the age of 6 days, and remained asymptomatic until the eighteenth day of life when he again began to vomit. At 30 days of age laparotomy was performed and a duodenal ulcer was found to be producing duodenal obstruction. A gastrojejunostomy was performed. The subsequent course was uneventful. The jaundice, which persisted until the age of 35 days, may have resulted from the absorption of blood from the bleeding duodenal ulcer.

Hematemesis and melena in the newborn period in most instances is due to blood that has been ingested

either at the time of delivery or subsequently from a bleeding nipple while nursing at the breast. However, in those instances where the hemoglobin, extracted from the blood being passed orally or rectally, is found to be alkaline resistant, the blood can be assumed to be from hemorrhage and not ingested blood.[2]

About 0.2 per cent of infants studied at autopsy have peptic ulcers.[3] They have been found in stillborns.[3] In one case perforation occurred during the intrauterine period.[4] However, intestinal obstruction resulting from a duodenal ulcer is extremely rare in the neonate.

Disorders of the respiratory or central nervous systems, burns, septicemia, and external trauma have all been implicated as causes of peptic ulcers in the neonate. These conditions are more commonly associated with gastric ulcers than duodenal ulcers.[3, 5, 6] The increased output of hydrochloric acid shortly after birth[7, 8] may play some role in producing a greater incidence of ulcers at this age as compared with later infancy.

In young children the therapy of peptic ulcers and their complications should be as conservative as possible. This is particularly true in the newborn period since newborn infants recovering from peptic ulcers rarely have a recurrence. If surgery becomes necessary because of bleeding, gastrectomy should be avoided and the bleeding site should, when practical, be attacked directly. Gastrojejunostomy is the treatment of choice if surgery is required for obstruction.[5]

SUMMARY

A case of duodenal ulcer producing intestinal obstruction during the neonatal period has been presented.

I wish to thank Dr. Henry K. Silver for his assistance in preparation of the manuscript.

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CELLULITIS OF THE LEG DUE TO TYPE B HEMOPHILUS INFLUENZAE

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INFECTIONS of the respiratory tract due to type b *Hemophilus influenzae* are not rare,[1-5] and when bacteremia or septicemia with the organism occurs, remote infections of other tissues can result. The most frequent type of remote hematogenous infection is meningitis, but other unusual types of *Hemophilus influenzae* infection have been reported. Next to meningitis, pyarthrosis appears to be the most frequent, with 16 definite and 9 probable infections of this type documented in the literature.[6-8] Pericarditis due to type b *Hemophilus influenzae* has been reported in 13 patients.[9-11] Six cases of cellulitis associated with Hemophilus infection were reported by Green and Fousek.[12] In 4 of these cases there appears to be no doubt as to the etiology of the infection. Earlier reports by Alexander[13] cited one child with cellulitis of the neck due to *Hemophilus influenzae* and with progression to meningitis. Tomic-Karovic[14] reported a single case of cellulitis of the neck due to this organism and was able to locate one previous and similar case in the European literature. Thus, 7 cases of cellulitis appear definitely to be the result of a *Hemophilus influenzae* infection. Hemophilus osteomyelitis is even more rare. While most texts mention this organism among the causes of acute osteomyelitis in infancy and childhood, the single case mentioned by Green and coworkers[15] is the only definite instance located in over 800 reported cases of childhood osteomyelitis in recent years.

Because of the rarity of type b *Hemophilus influenzae* cellulitis, the following case of an isolated cellulitis in the leg of an infant is reported.

CASE REPORT

The patient, a 6-month-old white boy, was delivered without incident after an uncomplicated full-term pregnancy. The neonatal period was uneventful and, with the exception of a mild diarrhea at age 5 months, the infant had enjoyed good health. He had received 3 triple-antigen injections between 2 and 4 months of age, and had been successfully vaccinated three weeks prior to the onset of the present illness.

On Jan. 27, 1958, the child appeared lethargic and was noted to have a fever of 103° F. On the following day the fever rose to 104° F. and the infant appeared acutely ill. For the first time the mother noted that he was irritable when the left leg was moved. Two days later, his fever had remained the same, and the left leg was swollen from mid-thigh to mid-leg. The leg appeared red and was warm to the touch. The infant was hospitalized at this time.

Physical examination revealed an acutely ill infant whose temperature was 104.9° F. His respiratory passages were not inflamed. The anterior fontanel was open and soft, and there

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was no nuchal rigidity. Examination revealed that the chest was within limits of normal, with the exception of a moderate sinus tachycardia (pulse 138). The examination of the abdomen was negative. There were no localizing or lateralizing neurologic signs. The infant's left leg was markedly swollen from a point two inches above the left knee down to, but not including the ankle. The skin was bright red in color, and the margins of the swollen area had an erysipeloid appearance. There was moderate inguinal lymphadenopathy. The swollen area of the leg was warm to the touch. No skin lesions or evidence of previous injury to the leg or foot could be found. Movement of the left leg caused extreme pain. The left knee, held in a position of extension, could be flexed no more than 10 to 15 degrees.

On admission the infant's hemoglobin was 10.6 Gm./100 ml. The red blood cell count was 4.39 million cells per cubic millimeter. The white blood cell count was 22,450 cells per cubic millimeter, with 70 per cent polymorphonuclears. Urinalysis was normal. Culture of the nasopharynx revealed *Hemophilus influenzae*, type b, *alpha streptococci*, and *Escherichia coli*. The blood culture, taken on admission, revealed a heavy growth of *Hemophilus influenzae*, type b. The organism was highly sensitive to tetracycline, novobiocin, and chloramphenicol, moderately sensitive to streptomycin, and resistant in vitro to all other antibiotics. Lumbar puncture on admission revealed a clear fluid with 5 mononuclear cells per cubic millimeter, a total protein of 14.4 mg./100 ml., and no bacterial growth on culture. The roentgenogram of the left leg showed soft tissue swelling only. An attempt was made to aspirate the left knee joint but no fluid was obtained, and culture of the needle tip revealed no bacterial growth.

On admission to the hospital, and before results of the initial cultures were known, the infant was started on intravenous penicillin (2.4 million unit a day), intravenous chloramphenicol (40 mg. per kilogram per day), oral novobiocin (20 mg. per kilogram per day), and oral sulfadiazine (0.15 Gm. per kilogram per day). When culture results were obtained, sulfadiazine and i.v. penicillin were discontinued. After three days of therapy the swelling of the left leg commenced to subside, and the infant's temperature, which had ranged from 102 to 104.6° F., fell slowly to normal. Intravenous antibiotic administration was discontinued in favor of oral chloramphenicol, and after a total of two weeks of therapy, the infant was discharged with apparent complete recovery and with full motion of the left knee joint. A repeat lumbar puncture at the time of discharge showed no cells in the spinal fluid. The roentgenogram of the left leg two weeks after the onset of the illness showed no abnormality in the bone, and a final roentgenogram three months after discharge from the hospital was also negative.

DISCUSSION

Recovery of type b *Hemophilus influenzae* from both the nasopharynx and from the blood of this patient leaves no doubt as to the bacteriologic etiology of the cellulitis observed. Pyarthrosis can be excluded on the basis of the negative results of aspiration of the left knee joint. It seems unlikely, in view of the negative roentgenograms of the left femur, tibia and fibula, that osteomyelitis existed. While, of course, an early minimal osteomyelitis cannot be entirely excluded, the fact that no periosteal reaction was seen during the three months following recovery from the infection can be taken as reasonable evidence that infection of bone did not occur. The age of the infant is typical of that period of life when natural resistance is low, and acquired resistance is insufficient to prevent hematogenous

dissemination of virulent nasopharyngeal pathogens.[16]

SUMMARY

An isolated cellulitis of the leg in a 6-month-old infant was demonstrated to result from infection with a type b *Hemophilus influenzae* organism. Two other frequent, or rare, complications of hematogenous dissemination of this virulent pathogen in young infants such as meningitis, pyarthrosis, or osteomyelitis, were not seen in this case.

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HEMOGLOBIN S—HEREDITARY SPHEROCYTOSIS

Two Case Reports

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SINCE the advent of electrophoresis as a means of differentiating the hemoglobinopathies, sickle cell hemoglobin has been found in combination with C, D, and G hemoglobin.[1, 2] Sickle cell thalassemia mixtures have also been described.[1, 2] To date, only two patients have been reported with a sickle cell trait and hereditary spherocytosis.[3, 4] Recently, we have had the opportunity to study two such patients, both of whom had been treated for several years as though they had sickle cell anemia alone.

CASE REPORTS

Case 1.—C. W., a Negro boy, was first seen at the St. Louis Children's Hospital at 14 years of age, with a complaint of vomiting, headache, and dizziness of three days' duration. His illness began with severe upper abdominal pain while riding his bicycle, and was followed by shortness of breath, malaise, weakness, frontal headache, nausea, vomiting, and anorexia. The sclerae had been yellow for one week. Bilateral breast enlargement had been present for about one year.

The past history was significant in that he had been hospitalized on four separate occasions at another institution for blood transfusions. The presumptive diagnosis was sickle cell anemia. Laboratory data during these admissions showed hemoglobin counts of 7.4 to 10.0 Gm./100 ml., red blood cell counts of 2.20 to 2.90 million, and reticulocyte counts of 9.5 to 10.0 per cent.

Physical examination on admission revealed a well-nourished, pubertal Negro boy with definite scleral icterus and moderate bilateral gynecomastia. The left border of the heart was percussed at the anterior axillary line, and there was a Grade 2 systolic murmur heard best in the second left intercostal space. The spleen was palpable about 9 cm. below the left costal margin and was very firm but not tender. The examination was within normal limits otherwise.

Laboratory data were as follows: hemoglobin 9.9 Gm./100 ml., red blood cell count 3.31 million, hematocrit 28 per cent, mean corpuscular volume 81 $c\mu$, mean corpuscular hemoglobin 29 $\gamma\gamma$, mean corpuscular hemoglobin concentration 36 per cent, and reticulocytes 13.9 per cent. The total serum protein was 6.50 Gm./100 ml., with 4.9 of albumin and 1.60 of globulin. Total bilirubin was 4.7 mg./100 ml., with 0.5 mg. of direct reacting bilirubin. Direct Coombs test was negative. Nonprotein nitrogen was 22, and the cephalin flocculation was 3 plus in 24 hours and 4 plus in 48 hours.

A bone marrow aspiration showed a very cellular marrow with a normoblastic erythroid hyperplasia. There was normal maturation of the myeloid series and megakaryocytes. Many of the red cells were spherocytic.

As is shown in Table I, hemoglobin electrophoresis revealed SA hemoglobin, and the fetal hemoglobin constituted 5.2 per cent of the total. The peripheral blood smear was striking in that many spherocytes were present.

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The osmotic fragility test showed beginning hemolysis at 0.80 per cent NaCl and complete hemolysis at 0.40 per cent NaCl as compared with a control of 0.44 to 0.36 per cent NaCl.

The hematologic data on the remainder of the family are summarized in Table I.

TABLE I. SUMMARY OF HEMATOLOGIC DATA OF THE FAMILY OF CASE 1

	HEMOGLOBIN (GM./100 ML.)	ELECTROPHORESIS	FETAL HEMOGLOBIN (PER CENT)	SALINE FRAGILITY (BEGINNING)	SALINE FRAGILITY (COMPLETE)	SPHEROCYTES
Patient	9.9	SA	5.2	.80	.40	Yes
Father	13.7	SA	0	.40	.32	No
Mother	11.9	AA	0	.44	.36	No
Sister	12.5	SA	0	.46	.36	No

TABLE II. SUMMARY OF HEMATOLOGIC DATA ON THE FAMILY OF CASE 2

	HEMOGLOBIN (GM./100 ML.)	RETICULOCYTES	ELECTROPHORESIS	SALINE FRAGILITY (BEGINNING)	SALINE FRAGILITY (COMPLETE)	SPHEROCYTES
				Control 0.40	0.32	
Patient	4.9	9.7	SA	0.56	0.36	Yes
Mother	9.5	9.2	AA	0.56	0.36	Yes
Maternal half brother 11 years old	11.0	1.5	AA			No
Maternal half brother 9 years old	10.7	2.0	AA			No

Two weeks after admission, a splenectomy was performed and the postoperative course was uneventful. One week following surgery, he had a hemoglobin count of 12.0 Gm./100 ml., a red blood cell count of 4.50 million, and reticulocytes of 4.3 per cent.

The spleen weighed 560 grams and showed moderate congestion. Erythrocytes were packed into the splenic pulp. Many of the erythrocytes were sickled. The sinusoids were collapsed or only partially filled.

Follow-up visits revealed normal peripheral blood counts although spheroeytosis persisted.

CASE 2.—D. R., a Negro girl, was admitted to the St. Louis Children's Hospital at 13 years of age, complaining of headache, weakness, dizziness, and "yellow eyes" of 36 hours' duration. The day preceding the onset of these symptoms, she experienced vague abdominal discomfort.

This girl had been admitted to another institution on eight occasions for blood transfusions. She had had one previous admission here, where a hemoglobin of 4.8 Gm./100 ml. was found. Laboratory data from the other hospital showed hemoglobin values ranging from 4.3 to 8.1 Gm./100 ml. Splenomegaly had been noted on several occasions.

Physical examination revealed a thin Negro girl with moderate scleral icterus. Mucous membranes were pale. The heart was slightly enlarged to percussion, and there was a soft Grade 1 apical systolic murmur. The liver edge was palpable at the right costal margin. The spleen was palpable 10 cm. below the left costal margin and was firm and nontender. The examination was not remarkable otherwise.

Laboratory data revealed the following: hemoglobin 4.9 Gm./100 ml., hematocrit 13 per cent, red blood cell count 1.56 million, mean corpuscular volume 83.3 $c\mu$, mean corpuscular hemoglobin 31.4 $\gamma\gamma$, mean corpuscular hemoglobin concentration 37.1 per cent, reticulocytes 9.7 per cent, and a

normal platelet count. The total bilirubin was 6.2 mg./100 ml., with a direct reacting fraction of 0.6 mg./100 ml. Total protein was 7.00 Gm./100 ml., with an albumin of 4.88 Gm./100 ml. and a globulin of 2.12. Prothrombin time was 70 per cent of normal, and the cephalin flocculation test was negative. Alkaline phosphatase was 5.7 Bodansky units.

The peripheral blood smear showed a moderate number of spherocytes. A metabisulfite sickle cell preparation was positive, and paper electrophoresis revealed SA hemoglobin. The hematologic data on the available members of the family are shown in Table II. The osmotic fragility test on the patient showed beginning hemolysis at 0.56 per cent NaCl as compared to 0.40 per cent NaCl in the control, and complete hemolysis at 0.36 per cent NaCl as compared to 0.32 per cent NaCl for the control.

A splenectomy was performed ten days after admission, which was followed by an uneventful recovery. The spleen weighed 620 grams. The splenic sinusoids were engorged, and erythrocytes were abundant in the splenic pulp. Deposits of hemosiderin were present.

Since surgery, blood counts have been normal with hemoglobin counts of 12 to 13 Gm./100 ml. and reticulocyte counts of less than 1 per cent. The spherocytosis persists.

DISCUSSION

Hereditary spherocytosis is relatively rare in Negroes. To date, 19 cases[5-13] have been reported and of these, 15 were females and only 4 were males. Our first patient was interesting in that no spherocytosis or increase in osmotic fragility could be demonstrated in either parent or in the sibling. Young and his colleagues[14] reviewed the inheritance pattern in hereditary spherocytosis and suggested four possible explanations for a failure to detect the disease in either parent: (1) minor degrees of penetrance or expression, making its presence undetected with present methods, (2) mutation, (3) atypical acquired hemolytic anemia, and (4) illegitimacy.

The predominance of females is probably a chance finding due to the small series since no sex linkage has been suggested in this disorder.

It is of practical importance to separate the patients with a sickle cell hereditary spherocytosis from those with sickle cell anemia. The striking physical finding in the former is a marked splenomegaly, but, also, young children with sickle cell anemia frequently have splenomegaly. In sickle cell anemia the spleen is larger during a crisis than during a quiescent phase. As these patients approach adulthood, the spleen gradually decreases in size until it is no longer palpable. It is rare to find a palpable spleen in an adult who has sickle cell anemia.

Spherocytosis, of course, is not found in sickle cell anemia or trait, nor is an increase in saline fragility demonstrable. Hemoglobin electrophoresis in our patients repeatedly revealed an SA pattern. This finding in patients with repeated episodes of jaundice, anemia, and reticulocytosis immediately suggests that a hemolytic mechanism other than sickle cell trait is present since such episodes have not been reported to occur in sickle cell traits. Splenectomy eliminates the repeated episodes of anemia and jaundice in patients with hereditary spherocytosis, whereas it is of no benefit in sickle cell anemia.

SUMMARY

Two cases of sickle cell hereditary spherocytosis have been presented.

The repeated episodes of hemolysis were alleviated by splenectomy. Family studies are also described.

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Clinical Pathological Conference

The Children's Medical Center
Boston, Mass.

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THIS girl, at the age of $3\frac{3}{12}$ years, developed fever and a painful left ankle. She was admitted to a hospital one week after the onset of her symptoms, where she was noted to have a temperature of 104° F., a widespread macular erythematous rash, and a grade II systolic murmur along the left sternal border. Her serum antistreptolysin titer was less than 50 U. and her corrected sedimentation rate was 38 mm. per hour, but her electrocardiogram and other laboratory studies were normal. During her course she displayed a migratory arthralgia which disappeared rapidly, as did her fever, after the administration of aspirin. After a 12-day hospital stay, she was discharged, considerably improved.

For the following eight months she remained at home, with a low-grade fever. Seven months after her hospital discharge she was placed on Meticorten.

At the age of $4\frac{1}{12}$ years, she was admitted to a second hospital, where she received cortisone, 200 mg. daily, which was replaced by Meticorten, the dose of the latter being reduced gradually over a year's interval to 10 mg. per day. She developed a marked Cushing habitus on this regime.

At the age of $4\frac{11}{12}$, after being on an 8-day regime of 9 Bufferin tablets daily, and while weighing 35 pounds, she developed nausea, vomiting, and rapid respirations. Her serum salicylate level then was 51.2 mg. per cent. Over the next 29 hours she received 2,100 ml. of 5 per cent dextrose in water, and 400 ml. of normal saline. She then had a convulsion and was transferred to The Children's Medical Center. At the time of admission, 3 hours after her first convulsion, she was still convulsing, with more marked signs on the left side. Her vital signs were: temperature 100° F., blood pressure 140 mm. Hg systolic and 40 mm. Hg diastolic, pulse 140, and respirations 28 per minute. She was diffusely edematous, and moist râles were heard throughout both lung fields, though the neck veins were not distended. The liver was felt two fingerbreadths below the costal margin. The remainder of the physical examination was negative.

Laboratory examination gave the following results: serum pH 7.0, carbon dioxide content 12, sodium

123, potassium 5.4, and chloride 9.8 mEq. per liter. The serum nonprotein nitrogen was 27, and sodium salicylate level was 10 mg. per cent. The urinalysis yielded: pH 5.0, specific gravity 1.001, albumin—trace, sediment—a rare hyaline cast. The blood hemoglobin was 10 Gm. per cent, the leucocytes numbered 40.9 thousand per cubic millimeter. Cultures of the nose and throat yielded a few colonies of *Staphylococcus aureus*. The chest roentgenograms showed an enlarged cardiac silhouette, pulmonary congestion, and markings consistent with bronchopneumonia.

The patient responded to therapy with sedation, digitalis, and antibiotics. She was returned to the referring hospital ten days after admission.

At the age of $5\frac{8}{12}$ years, therapy with chloroquine, 250 mg. daily, was begun. Five days after the initial administration, a routine urinalysis showed the presence of a marked albuminuria. Meticorten was substituted for the chloroquine. Twelve days later, the 4 plus albuminuria persisted; the total serum protein was 6.0 Gm., albumin 1.8, globulin 4.0, of which gamma globulin was 2.44 Gm. per cent as determined by electrophoresis. The cholesterol level was 222 mg. per cent. An "L. E." preparation was negative.

The patient was readmitted to The Children's Medical Center at $5\frac{9}{12}$ years for the second time. She appeared chronically ill and poorly nourished, with a macular rash over the arms, neck, and thorax. Motion of the neck in any direction produced pain. The large joints of both the arms and legs were swollen and painful. The proximal interphalangeal joints of the fingers were markedly swollen; those of the toes were less affected. The liver was palpable 1.0 cm. below the right costal margin, but neither the spleen nor the kidneys were felt. There was no generalized edema.

Urines studied at this time had pH values of 6.0 and 7.0, specific gravities of 1.015 and 1.022, albumin 2 to 3 plus, sugar absent to trace, erythrocytes 0 to 3, and leukocytes up to 4 to 5 per high power field. The hemoglobin was 11.5 Gm. per cent, the hematocrit 38 per cent; the leukocytes numbered 31.2 thousand per cubic millimeter. The differential smear showed: polymorphonuclear cells 85, lymphocytes 13, and monocytes 2 per cent. The platelets were adequate, and erythrocytes morphologically normal. The serum chemistry values were: sodium 138, potassium 5.0, and chlorides 103 mEq. per liter, nonprotein nitrogens 29, calcium 9.6, and phosphorus 7.0 mg. per cent. The serum protein was 4.6 per cent, and the corrected sedimentation rate 40 mm. per hour.

The day after admission a renal biopsy was performed.

DR. GERTRUD C. REYERSBACH.*—This child's illness began at the age of 3 years with a fever which went as high as 104° F., and painful ankles. She then very quickly developed migratory arthritis and a macular erythematous rash. She also had, at that time, a systolic murmur. I think one might assume that this was a functional murmur, because it was never mentioned again. An electrocardiogram was normal.

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The laboratory findings included an elevated sedimentation rate and an antistreptolysin titer of 50. We aren't told what the leukocyte count was, but it was probably high.

It seems to me that the physicians who took care of her at that time had to decide whether this child had rheumatic fever or rheumatoid arthritis. I would also guess that the choice of diagnosis was not particularly difficult. Rashes may be present in both diseases; in rheumatic fever one usually finds an elevated antistreptolysin titer due to a preceding streptococcal infection. If a child has as much fever and as much arthritis as this child had, due to rheumatic fever, there are cardiac findings. I think a diagnosis of rheumatoid arthritis was made.

The child improved to such an extent on aspirin that she was sent home for six months—whether on aspirin or not, we are not told. We know that she ran a low-grade fever and may surmise that she was anoretic, listless, and probably had more joint involvement because after six months Meticorten was given at home in doses of 2 to 5 mg. twice a day—hardly an effective dose. On the other hand, steroid therapy in adequate doses is dangerous to administer at home. She was readmitted to the referring hospital so that she might be treated with an adequate amount of cortisone. While the steroid dose was such that it made the little girl Cushingoid, it does not seem to have controlled the disease completely, and aspirin in the form of Bufferin was added to the regime. The combination of aspirin and cortisone may work better than either drug alone.

Up to the point of her last admission to The Children's Medical Center, I think she presents a typical picture of rheumatoid arthritis. She was chronically ill, poorly developed and nourished, and had skin rashes. The joints of the arms and legs were swollen and painful; the proximal interphalangeal joints were involved, as was the cervical spine. She had evidently escaped certain other manifestations which this disease can produce—namely, subcutaneous nodules, pericarditis, or generalized lymphadenopathy. The spleen was not enlarged, and there was no involvement of the uveal tract of the eyes, which is not infrequent. If x-rays were taken of the child's joints at this time, they should show the changes of rheumatoid arthritis, and I wonder whether there are any.

DR. E. B. D. NEUHAUSER.—We have none available up to this point.

DR. REYERSBACH.—Well, I shall assume that they were typical of the disease. I would like to go to the treatment for this disorder as we have seen it here. Tetracycline, penicillin, and all other antibiotics which might be used have been singularly ineffective in changing the course of the disease, but aspirin has remained the standby for a good number of years; it reduces the fever, and its analgesic effect abolishes joint pain. This makes the child more comfortable and allows more active physical therapy to prevent contractures. It has been shown that steroids suppress the manifest symptoms of rheumatoid arthritis very well indeed, but the initial enthusiasm for their use has waned somewhat. In England,[1] there was a trial in the treatment of 25 children

with juvenile rheumatoid arthritis by either aspirin or cortisone. The children were given 12-week courses of therapy; if symptoms recurred, they were retreated for 12 weeks; later they were treated continuously with the minimum dose which would control symptoms. The children were reappraised after a year, and no real difference could be found in the children who had received aspirin and those who had received steroids. Many of them were improved, but they might have improved on their own. Toxic reactions in the aspirin group were quite rare, and while the 13 children on cortisone did not have many toxic effects, there was one patient with a collapsed dorsal vertebra, one with inconstant glycosuria, and one who developed hypertension.

The patient's admission to The Children's Medical Center seems to have been due to salicylate poisoning and water intoxication. The salicylate level of 51 mg. per cent clinches the former diagnosis. The therapeutic salicylate level generally is 20 mg. per cent. Toxic symptoms were nausea, vomiting, and "rapid respirations," which I interpret as having been hyperpnea. The central stimulating effect of salicylate produces hyperpnea and a respiratory alkalosis in the beginning; later there is believed to be a true acidosis. The treatment of this disorder by intravenous fluids is complicated by the fact that salicylates tend to increase the circulating plasma volume. This child was given 2,500 c.c. of fluid in 29 hours. The 400 c.c. of normal saline was probably given in the beginning in an attempt to correct the alkalosis; then she was given 5 per cent dextrose in water. The latter is isotonic as it enters the blood stream, but the dextrose is very quickly metabolized and then free water is left. If there is too much, it tends to enter the cells and approximately one-third of it will go into the extracellular fluid. The amount given here was such that I think it is fair to assume that the child had water intoxication. The treatment was successful in one respect, in that the salicylate level dropped to 10 mg. per cent. When the child was admitted here, she had convulsions, which are frequent in water intoxication. The blood pressure of 140/110, I think, is consistent with that syndrome. The serum chemistry values as given are not completely characteristic; the sodium is usually lower than 120 mg. per liter. Generalized edema and pulmonary congestion are not features of ordinary water intoxication. One has to remember that this patient had been given steroids, and there may have been excess sodium stored away in this child. It will be my assumption that it was this sodium which attracted water, made her generally edematous, and gave her cardiac failure. Her urine specific gravity of 1.001 showed that the child was trying hard to get rid of this excess water. The usual treatment of mild water intoxication is just not to give any water and to let the child take care of himself. If the disease is more serious, one uses hypertonic saline. In this case, sodium bicarbonate was given intravenously, which may have been an attempt to facilitate the excretion of salicylate or to correct the acidosis. May we see the x-rays at this time?

DR. NEUHAUSER.—This film, Dr. Reyersbach, was made at that time—quite early in the course. Then the heart was considerably enlarged; it was globular and dilated. The lungs were slightly congested, and on the lateral films you can see a small amount of fluid in each costophrenic angle. In the next film, at the time of the last admission, the heart was about normal in size, but there was still a fluid collection right at the base. The lungs were clear. The only other x-ray change of interest which can be seen is the marked osteoporosis of the head of the femur.

DR. REYERSBACH.—Chloroquine, which was given, is an antimalaria drug which has been used in the treatment of disseminated lupus erythematosis. Pillsbury and Jacobson[2] described two people with generalized disseminated lupus erythematosis, in whom they thought they obtained good results with the administration of first 500 mg. and then 250 mg. daily of chloroquine. Evidently, lupus erythematosis was suspected in this little girl, in spite of the negative L. E. preparation. It was rightly concluded that one negative L. E. preparation did not exclude the diagnosis. Fairly large doses of chloroquine were given for four days, until albuminuria was discovered. Chloroquine may produce quite a few toxic symptoms, including rash, gastrointestinal and visual disturbances, but injury to the kidney, to the best of my knowledge, is not one of them.

I was interested to find that with a specific gravity of 1.002 at her previous entry, this child had demonstrable albuminuria, which means that she must have had considerable albuminuria. When the disease had run for two and a half years, she was readmitted to this institution for reevaluation. The question probably was—did she have rheumatoid arthritis with the complication of amyloidosis to explain the kidney findings, or did she have lupus erythematosis?

Secondary amyloidosis is not an infrequent complication in rheumatoid arthritis. Review of the literature reveals that of the patients with rheumatoid arthritis who have come to autopsy, more than 15 per cent have amyloidosis. Deposits are found chiefly in the liver, kidneys, spleen, and adrenals, but may also be found in the intestines and parathyroids. It doesn't seem to do much harm anywhere but in the kidneys, where it leads clinically, first, to massive albuminuria, to a reversal of the albumin/globulin ratio, and to a high gamma globulin level, which incidentally can occur without amyloidosis in rheumatoid arthritis. Quite a number of the children with severe rheumatoid arthritis die of amyloidosis. Amyloidosis has not been described in mild rheumatoid arthritis, but only in severe rheumatoid arthritis, such as this child had. Amyloidosis may be a reversible process, since patients have been described who have had amyloidosis, demonstrated by the Congo red test, and later recovered. It has been advocated that such people be given large amounts of crude liver in order to help them clear their amyloid deposits.

The diagnostic points in favor of amyloidosis, in summary, are: the whole clinical course, the normal blood pressure, the massive albuminuria, good renal function, and the

intimate relation with severe rheumatoid arthritis.

The operation, I presume, was a biopsy of the kidney, in order to establish a diagnosis of what I believe is amyloidosis, secondary to rheumatoid arthritis.

The other diagnosis which is suggested by the patient's course is lupus erythematosis disseminata. Lupus is known to attack chiefly young women, and is rare under the age of 15, but may appear as early as 2 years of age. The diagnostic points in favor of lupus are: the sex of the patient, the microscopic hematuria which was described on the last admission, the high gamma globulin (though that is certainly not specific), the heart failure, the erythema and the periorbital swelling. Against this diagnosis are the absence of leukopenia, or thrombocytopenia. There was no facial rash, and the blood pressure and kidney function were normal. The onset was not related to exposure to the sun, since she became ill in April.

DR. CRAIG.—How would you exclude the nephrotic syndrome—a membranous glomerulonephritis—in this patient? She doesn't have hypertension; she has had no macroscopic hematuria, but considerable albumin.

DR. REYERSBACH.—She had no urinary casts and I think these are very frequent in nephrosis. She had some microscopic hematuria described on the last admission. It seems peculiar that she should develop this syndrome on cortisone therapy. It has been postulated by some that the exhibition of cortisone as well as ACTH, at least in mice and rats, predisposes to the development of amyloidosis. I thought, for these reasons, amyloidosis was a more likely diagnosis.

DR. CRAIG.—Do you consider the amount of Bufferin that she received was toxic to her because of her renal difficulties?

DR. REYERSBACH.—No. I think that she received a very large dose. It represents about 2.7 Gm. of aspirin a day. This is really a tremendous dose for a child who weighs 16 kilograms, even with normal kidneys.

DR. CHARLES A. JANEWAY.—I wondered if you could tell me how frequently (in the days before we had all these tools to make it possible for us to make a child sicker than the disease already has) amyloidosis developed in rheumatoid arthritis within two and a half years from its onset?

DR. REYERSBACH.—This is not infrequent. It was described first in association with rheumatoid arthritis in 1903, I think, simultaneously in the United States and in Germany. Amyloidosis has been reported as early as six months after the onset of arthritis, and this before we had cortisone and ACTH. I think that it is inherent in rheumatoid arthritis.

A STUDENT.—Would the osteoporosis have any relation to the combination of the processes here?

DR. REYERSBACH.—Osteoporosis occurs, even if the disease is a benign one. It is inherent in the rheumatoid process.

DR. JANEWAY.—One of my clearcut recollections as a medical student was a visit to the Montreal General Hospital where I saw my first case of

this disease. I was told that the patient was being given liver extract and that this was very good for her.

DR. REYERSBACH.—Yes, such a report did emanate from Montreal and such therapy was then tried in New York, but no more good results were obtained on further trial.

DR. CRAIG.—You mentioned some relation of the amyloid to the gamma globulin. Is the gamma globulin elevated first, and is amyloidosis secondary?

DR. JANEWAY.—Dr. Gitlin and I have seen a case of primary amyloidosis with agammaglobulinemia. Amyloidosis develops, as is well known, in animals after long immunization procedures with the development of high levels of gamma globulin. There may be polymerization of the gamma globulin molecules which cuts down on the osmotic pressure of the increased protein content of the serum. The serum proteins in rheumatoid arthritis, as has been known for many years, have the capacity to agglutinate nonspecific antigens. The glycoproteins are also very much elevated in amyloidosis. The term, of course, refers to the fact that it contains some carbohydrate.

DR. CRAIG.—A kidney biopsy was done and very early, but typical findings of amyloidosis of the kidney are found. The tubules are considerably dilated, filled with proteinaceous precipitate, and lined by rather narrow epithelial cells. In the glomeruli there are rather marked focal thickenings of an area of the basement membrane, more particularly lying

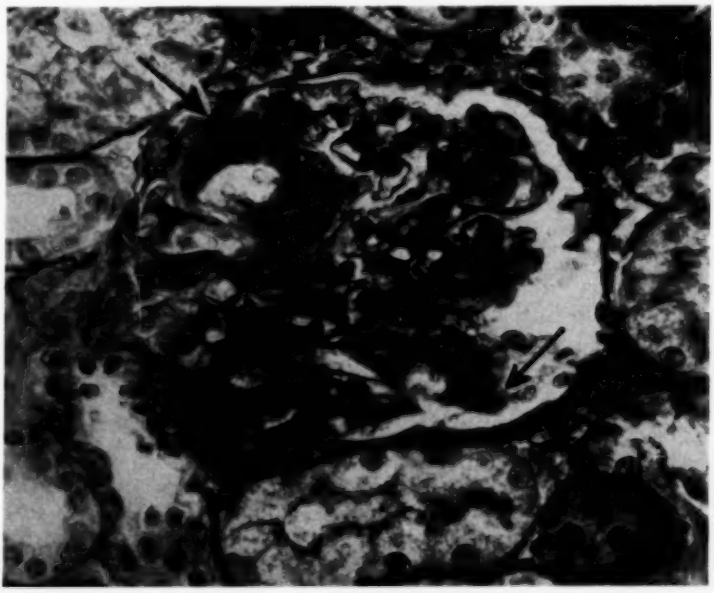

Fig. 1.—Focal deposits of amyloid in the renal glomerulus are present at the arrows in the capillary walls. (Toluidine blue and eosin ×600.)

between the endothelium and the basement membrane (Fig. 1). The amyloid deposits have a focal or lobular character and occasionally stain positively with the periodic acid-Schiff technique. This case isn't very far advanced and there are no secondary ischemic degenerative changes in the renal tubules. There is no evidence of deposition of amyloid in the tubular areas, but there may be some in the afferent vessels.

Dr. Reyersbach indicated that certain of these patients do have the possibility of recovering, but in general the prognosis is extremely poor. In a review in 1944,[3] a single acceptable case was cited which went on to recovery. The established mortality of the process is well over 90 per cent, and often progression is very rapid once the syndrome develops, with death resulting from renal failure and uremia.

I do not know what this child's course has been since the biopsy.

DR. MICHAEL BRAUDO.—This child was readmitted to this hospital for the third time in January of this year because of convulsions, massive edema, low sodium and high phosphorus values. We subsequently attributed this convulsion to cerebrovascular accident or water intoxication. During this hospital stay she also had low sodium and chloride serum values. She was treated with intravenous albumin and was discharged in fairly good condition, having lost her edema. Not mentioned in the protocol, for obvious reasons, was a positive Congo red test, showing complete retention of the dye.

DR. CRAIG.—There have been attempts to demonstrate gamma globulin in the amyloid deposits by the Coons' fluorescent antibody technique, particularly by Vasquez and Dixon,[4] and also by Wagner.[5] They have, to their satisfaction, demonstrated the presence of gamma globulin in the amyloid deposits both in experimental work and in human tissue. Dr. Gitlin takes some exception to these findings, for working with Dr. Calkins and Dr. Cohen of the Massachusetts General Hospital,[6] using grinding and extracting procedures on amyloid-containing tissue, they have not been able to demonstrate the presence of gamma globulin in their extracts.

DR. ROBERT E. HAGGERTY.—What reliance, if any, can be placed on a biopsy of the gingiva to establish a diagnosis?

DR. CRAIG.—Well, I would think that in many cases you would miss it, since even in children who have died with amyloidosis, the amyloid may be deposited in one of the viscera and not in the others. You may have it in the liver and spleen, in the kidney alone, in the liver alone, or any combination of these. However, I think that in a certain proportion of cases, particularly in the secondary amyloidosis, a gingival biopsy may not show the presence of amyloid. I suspect that you are more apt to find a positive gingival biopsy in the primary form of amyloidosis where there is no known etiological agent, and the distribution of amyloid is more widespread. We have examined gingival biopsies on several occasions when the diagnosis has been suggested, and we have never been able to demonstrate amyloid in them.

DR. RANDOLPH K. BYERS.—In the neuropathy of primary amyloidosis, it has been shown repeatedly that the gingival biopsies are characteristically positive only in the primary cases and in only 25 or 30 per cent of these. The best place for evidence of amyloid in the primary disease is in the epiglottis.

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Comments on Current Literature

GLANDULAR TOXOPLASMOSIS

ALTHOUGH the protozoan parasite toxoplasma had been described as early as 1908 in a North African rodent, the gondi, and about the same time in the wild rabbit in Brazil, it was not established definitely until 1939 that the agent could produce disease in the human subject.[1] Clinical manifestations of the disease were recognized first in the form of congenital toxoplasmosis: encephalomyelitis in early infancy, usually with chorioretinitis. Typical manifestations of infection in the newborn infant included hepatomegaly, splenomegaly, icterus, maculopapular rash, chorioretinitis, and cerebral calcification, with the subsequent development of hydrocephalus, or microcephaly, a not uncommon result. While the congenital forms of toxoplasmosis have continued to be a striking manifestation of this infection, it has become increasingly apparent that the acquired postnatal form is common, and that the manifestations of this infectious process may vary widely: from inapparent infection to definite clinical disease, which includes meningoencephalitis, glandular involvement, or eye involvement. Clinical manifestations in some instances may simulate those of the rickettsial diseases.

A practical classification of toxoplasmic infection in human subjects, suggested by Beckett and Flynn[2] in 1953, serves to emphasize the wide variety of clinical manifestation for which the toxoplasma organism may be responsible: (1) a silent infection essentially asymptomatic; (2) a mild grippe-like infection similar in some respects to nonparalytic poliomyelitis; (3) a mild infection simulating infectious mononucleosis which is characterized by enlarged glands and slow convalescence, with eventual complete recovery, and with negative Paul-Bunnell test; (4) chorioretinitis; (5) an acquired systemic infection occurring in adults and children which gives rise to signs and symptoms of widespread disease. In this last category, the illness may be characterized by a rash which spares the scalp, palms of the hands, and soles of the feet, suggestive of acute rickettsial infection; by an encephalitis without visceral involvement; by chorioretinitis; or by a febrile illness suggesting widespread collagen disease. Congenital toxoplasmosis, discussed by these authors as a separate category, is divided further into two essential types with allowance for overlapping manifestations: (a) a severe febrile illness beginning in the immediate neonatal period with vomiting, convulsions, and nystagmus, followed by progressive hydrocephalus, chorioretinitis, and cerebral calcification, which is characteristically diffuse and spotty; and (b) predominant perinatal manifestations similar to those seen in erythroblastosis fetalis: jaundice and hepatosplenomegaly.

Of particular interest to the clinician is a glandular form of toxoplasmic disease, reported currently in medical literature, which contributes significantly to the etiologic diagnosis of lymphadenopathy of unknown origin. In Denmark, Siim[3] has encountered over 100 such cases, and estimates that toxoplasma infection

accounts for about 5 per cent of the cases of lymphadenopathy of unknown origin. In a recent issue of *Lancet* a report from the University of Sheffield appears; this report by Beverley and Beattie[4] is entitled "Glandular Toxoplasmosis: A Survey of Thirty Cases." Earlier studies by Beattie[5] which were based on antibody titers had indicated that in the areas surveyed subclinical infection with toxoplasma was relatively common. In Lincolnshire, for example, 36 per cent of the country-dwellers and 22 per cent of the town-dwellers had dye-test antibodies (Sabin-Feldman) to a titer of 1:16, or higher. In the more recent clinical studies also, Beverley and Beattie made use of the Sabin-Feldman[6] dye test for the diagnosis of active infection, following the principle that the dye-test titer should increase eight-fold, or more, at least to a level of 1:256. In the presence of active infection, the titer will be maintained at or near this level for several weeks. In addition to the dye test, the authors have employed complement-fixation antibody procedures for verification, and state that "the level of the complement-fixing antibody should either change from negative to positive and rise to a titre of ⅛, or, if positive initially, should subsequently increase at least four-fold."[4] For purposes of this recent clinical study, Beverley and Beattie adopted an arbitrary level of 1:256 for the dye-test titer, and a complement-fixation titer of 1:10, the results obtained being correlated wherever possible with search for the toxoplasma organism. In 4 of the 30 cases described, toxoplasma organisms were isolated from excised glandular tissue by the inoculation of mice. As the authors emphasize, these organisms when obtained from man often prove of low virulence for laboratory animals. However, in some instances in which the animals are free of objective signs, toxoplasmic cysts may be seen in the brains of inoculated animals for as long as a month, or more, after inoculation. This problem of low virulence in relation to exact etiologic diagnosis may be solved to some extent by the use of methods more recently developed: inoculation of the embryonated egg and of tissue culture preparations.[7] It is difficult also to detect the parasite in stained sections of lymph glands excised from human subjects; after long search Stanton and Pinkerton[8] were able to report the finding of one cyst. Likewise, the pathologic changes observed in human lymph nodes are not characteristic, being described in some instances as a "lymphohistiocytic medullary reticulosis," and in others as a "focal medullary reticulosis."

In the cases of glandular toxoplasmosis reported currently, the initial clinical diagnosis most commonly considered was that of infectious mononucleosis. Other clinical impressions included tonsillitis, mumps, Hodgkin's disease, lymphosarcoma, leukemia, aleukemic leukemia, and poliomyelitis, indicating that the clinical manifestations are so varied as to be of little aid in diagnosis. None of the patients with glandular toxoplasmosis showed a positive Paul-Bunnell reaction. The age incidence is of interest: 10 of the 30 patients were under the age of 10 years, 11 patients were between the ages of 11 and 20 years, 4 patients ranged in age from 20 to 30 years, and 5 of the 30 patients were over 30 years of age. This age distribution is similar to the age incidence of infectious mononucleosis in children and young adults. The clinical manifestations of the disease process varied greatly in severity and duration. Some were never ill; others complained that they were "below par" for weeks. In 20 of the 30 patients, swelling and pain in the lymph glands (usually cervical) were noted initially. As a rule, these enlarged glands regressed very slowly, sometimes requiring many months for return to normal size. Sore throat, which was not a prominent symptom, was noted initially in only 7 patients, but developed later in the course in 3 others. Other symptoms

included severe headache, fatigue, depression, and muscle pain. From the clinical point of view, it is of interest that none of the 30 patients experienced high fever and 11 of them were afebrile. In some patients, pain in the neck and the back led to the suspicion of poliomyelitis, and in other instances meningismus was suspected. Several complained of pain in the joints and limbs and in some abdominal pain was present, suggesting some degree of mesenteric lymphadenitis. Fatigue was a common manifestation, and in some instances was long continued. Blood studies in 6 patients revealed an absolute leukocytosis; in 15 patients lymphocytosis was observed, and in 6, cells of the glandular-fever type were reported. In only one instance was there any suggestion of pulmonary involvement, and in one other instance enlarged hilar nodes were noted on x-ray examination. No serious sequelae were reported in this series of 30 patients.

The source of infection in human toxoplasmosis is not known definitely; animals have been suspected, since the organism is to be found in many animals and birds potentially associated with man: the gondi in Africa; mice, rats, rabbits, guinea pigs, squirrels, foxes, mink, chinchilla, dogs, cats, swine, sheep, cattle, various primates, as well as pigeons, chickens, ducks, and penguins.[9] The animals most commonly suspected are dogs, cats, and rabbits. In the series of patients with glandular toxoplasmosis currently reported from England,[4] 21 had association with dogs, in some instances close contact; 12 with cats, and 5 with budgerigars, a psittacine bird becoming increasingly popular as a pet. The significance of close association with animals or birds is indicated by the known occurrence of toxoplasma organisms in the droppings of birds, in the urine, feces, and saliva of animals, and also in the saliva of man. While the route of invasion in man is not known, it has been suggested that the organism may gain access to the body through the mucous membrane of the tonsillo-pharyngeal region, since cervical adenopathy is a common manifestation.

The widespread occurrence of toxoplasma infection in the human subject is reflected by surveys carried out on the human population in various parts of the world. Such a survey reported recently from the Toronto area by Harper, Ormsby, and Cockeram[10] indicates that positive skin test for toxoplasmin increases with age from about 10 per cent positive in the youngest age group studied to 40 per cent positive in the older age group. Also, the presence of complement-fixing antibodies in normal members of the population in this area would indicate that inapparent and unrecognized toxoplasmic infections are widespread. Thus, it appears that human infection with toxoplasma organisms is more common than has been supposed heretofore. Lymphadenopathy as a clinical manifestation appears to be one of the more common forms of acquired toxoplasmosis, and it seems reasonable that the various diagnostic tests for toxoplasmosis are indicated whenever the clinician encounters an unusual form of glandular involvement in the human subject. Since inapparent infection in the pregnant woman may result in abnormalities in the fetus, diagnosis would be of particular value in this group. The treatment of toxoplasmic infections has not been entirely satisfactory; reports in the literature, however, suggest that a combination of sulfadiazine and pyrimethamine, or triple sulfonamides plus pyrimethamine may be of value.[4, 9] Since pyrimethamine is a folic acid antagonist, and severe leukopenia may result from its use, leukocyte counts should be checked at frequent intervals in order to detect any adverse reaction to this drug.

The prevalence of toxoplasma infection among animals and birds would suggest that careful scrutiny be given the possible animal sources of human toxoplasmosis, particularly household pets. The recognition of toxoplasmosis as an infection widespread in the

human population, and current emphasis on the protean manifestations of this disease, including glandular involvement, particularly in the cervical region, should alert the clinician to this diagnostic possibility whenever unusual cases of glandular fever are encountered.

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Medical Progress

OBESITY IN CHILDREN

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OBESITY is common in children. Unlike poor appetite or hypophagia which has received much attention by pediatricians, excessive appetite or hyperphagia has been, in the main, neglected. Fortunately, a sizable proportion of overweight children slender down as adolescence approaches. There are several reasons for this: In girls a prominent consideration is a greatly increased interest in their appearance. Another consideration is that the rapid growth during adolescence often takes care of ingested calories and many children at this developmental stage grow up to their weight. In general, fat babies need be no cause for concern; they tend to lose their excess fat after the first year when the appetite normally falls off and activity increases.

However, obesity often persists. Children who become fat before the age of 10 years generally remain obese throughout life and are especially resistant to treatment as adults.

During the past two decades, views on the nature of obesity have changed fundamentally. Students of the subject no longer regard fat people as simply weak-willed, self-indulging gluttons who love their food immoderately or who eat excessively because of a distorted psyche. The attitude is growing that a prominent consideration in the genesis of obesity is a metabolic or constitutional predisposition. It is reasonable to assume that people vary in the efficiency with which they use ingested food, just as they vary in all other measurable attributes, and that the amount of utilizable energy derived from ingested food will not always be the same. It is becoming apparent, too, that the metabolic pathways for the utilization of ingested food differ in different individuals.

Observations on obese persons treated with low-calorie diets have yielded confusing results. While decreased intake results in weight loss, the amount of weight loss bears no simple relationship to the degree of calorie reduction. In the studies of Kekwick and Pawan,[12] high-fat reducing diets led to greater weight loss than isocalorie-high carbohydrate diets.

Ohlson[18] divided obese patients on low-calorie diets into two groups, those who were maintained in nitrogen balance and those who developed negative nitrogen balance even on high-protein reducing diets. The outlook for permanent weight reduction

was much poorer in the second than in the first group.

For a long time, breeders of farm animals have been aware of the variations in the efficiency with which food is used. The yield of milk, meat, eggs, lard, etc. per unit of ingested food varies enormously among different strains within a species, and farm animals are selectively bred to yield the greatest output for the least intake. Strains of high- and low-efficiency rats have been produced by selective breedings in the laboratory.

CONTROL OF HUNGER

Eating is principally controlled by the hypothalamus. The satiety center is in the medioventral nuclei of the hypothalamus. It acts as a brake on the stimulus to eat, which is located in the lateral areas of the hypothalamus.

Mayer[14] proposed that the influence of the metabolic state on feeding behavior and its role in regulating food intake were mediated through the rate of passage of glucose (or ions associated with it) into the cells of the ventromedial hypothalamic area. In man, the presence or absence of hunger contractions correlates well with arteriovenous differences in glucose, the contractions being slight or absent when the differences are large, indicating rapid utilization, and marked when the differences are small.

In favor of Mayer's view are experiments after the administration of glucagon, the pancreatic glycogenolytic factor. Glucose released by the breakdown of glycogen is well utilized and the arteriovenous difference in glucose is invariably increased. In all cases, gastric contractions and hunger sensations are promptly and strikingly eliminated.

The administration of gold thioglucose (a compound of gold and glucose) induces overeating and obesity. Presumably, the gold is drawn into the satiety cells by the glucose, for which the cells have a special affinity, destroying them. Compounds of gold other than with glucose do not have this effect.

Potassium enters the satiety cells together with the glucose, and this results in an ionic translocation which may be involved in the generation of electrical impulses to other centers in the central nervous system.

Other theories to explain the regulation of appetite are those of Brobeck[3] and Kennedy.[13] It is Brobeck's view that hypothalamic control of food intake is by the heat released during the metabolism of food. Kennedy has produced evidence of hypothalamic regulation by the amount of fat in the body, possibly through the circulating metabolites of fat.

ETIOLOGY

The etiologic mechanisms which may lead to obesity are multiple. Mayer divides them into (a) genetic, (b) hypothalamic, e.g., dystrophia adiposogenitalis, (c) other central nervous system disturbances, e.g., after frontal lobotomy, in association with cortical lesions, (d) endocrine, e.g., hyperinsulinemia of various sorts, Cushing's syndrome, and (e) miscellaneous, e.g., immobilization, psychic disturbances, and social and cultural pressure.

Heredity is a prominent factor in the etiology of obesity. A number of distinct genetic varieties may be recognized in animals. Among these

are: (1) a dominant, heterozygous type in which the animals are not only obese, but larger than their litter mates as well; (2) a recessive, homozygous type in which obesity is combined with hyperglycemia, hypercholesteremia, and certain behavior disturbances; (3) a genetic hypothalamic type in which the satiety mechanism is at fault.

Genetic factors have also been demonstrated in man. Obesity is markedly familial. Whereas less than 10 per cent of the children of parents of normal weights are obese, the proportion rises to 50 per cent when one parent is obese and 80 per cent when both parents are obese. Family habits of eating probably have some influence, but the dominant role of heredity is shown by studies on twins.

One-egg twins are more nearly alike in weight (r = .973) than in any other measurable attribute except height (r = .981). Verschuer[22] found that the mean difference in weight between one-egg twins was 5.7 pounds, and about 10 pounds between two-egg twins, the same as in siblings.

The mechanism of transmission is obscure.

The fact that heredity is a potent factor regulating the individual's body weight should not be interpreted as meaning that heredity fixes, minutely, optimal body weight. In the matter of weight regulation, as with other biologic attributes, the genetic endowment probably delimits a zone, rather than a point, within which the best weight for the individual fluctuates according to the food intake, activity, etc.

Psychologic Factors.—Bruch[4] divides obese people into 3 groups. The first group consists of persons in whom overweight is the normal state; they may be looked upon as normal variants at the upper end of the curve for the distribution of weight. A sample population of children, like adults, consists of a large number of persons with body weights which group themselves around the average, with a certain number on the thin side and a similar number on the fat side. The children on the fat side are most comfortable when they are well filled out. This is their natural make-up. They may or may not have emotional problems. If they do have problems, they may further increase their overweight. In addition they are apt to use their excess weight as a focus for self-belittling or as an excuse for their difficulties.

In the second group, referred to by Bruch as reactive obesity, overeating and its usual accompanying symptom underactivity are related to upsetting events. Obesity is the response to some traumatic, emotional experience. This type of obesity has been observed in children following the death of a sibling, death of a parent, separation of the parents, scholastic or social failure, birth of a sibling, or an operation. In a number of cases obesity has followed whooping cough.

In the third group, referred to by Bruch as developmental obesity, obesity must be regarded as one manifestation of a disturbed way of life which involves not only the child, but the whole family as well. Typically, the families consist of domineering, ambitious mothers and docile, acquiescent fathers. The families are small, usually consisting of one or two children.

Parental disharmony is the rule and there is much quarreling.

The fat child is kept unusually close to the mother who seeks to win his favor by plying him with food, thus keeping him from leaving her to join in the normal play activities of his peers. He is generally overprotected, often being unable to dress or bathe himself until adolescence.

The parents have an exaggerated idea of the amount of food which the child should eat. Many of them were poor in their youth and had often been hungry during their childhood. To them, giving food means safety and the satisfaction of their own longings, denied to them when they were children. Many of the parents are food handlers.

The father usually plays a secondary role, but in some instances he, too, assumes an attitude similar to the mother's. The essential pathological feature is that the child is used by one or both parents to satisfy their own emotional needs and as a compensation for failures and frustrations in their own lives.

In Bruch's experience an unusually high proportion of obese children are unwanted. In such instances the maternal emphasis on giving foods is an aspect of her guilt feelings—she tries to make up with food and other attentions what she is unable to give in affection.

The child contributes to the situation and is an active participant in it. He is dependent, submissive, and immature, and he uses these attributes to control his environment. He actually enjoys his helplessness and adheres to it stubbornly. His fundamental attitude toward the environment is demanding. He enjoys the pleasure and safety of infancy. Yet, he is not passive. He makes his claims and will not tolerate having them unsatisfied.

Bruch finds, further, that the child reacts not only with obesity, but with numerous defects in adaptation. As a result of deficient social relations, behavior is often "withdrawn" or "exclusive." Fat children tend to react to frustration by sudden withdrawal or hostility. There are strong feelings of helplessness, inadequacy, despair, and the conviction that they are ugly and unsightly.

Later, when such a child enters school and must adjust, for the first time, to the outside world, he is totally unprepared. Often he resorts to more eating, since food is for him his main source of comfort and satisfaction. In eating excessively he finds his principal outlet for aggressive and hostile feelings—it is the only way he knows for meeting traumatic experiences, failure, and disappointment.

Only later on, during adolescence or early adulthood, is there sufficient concern about the obesity so that help is sought and some degree of cooperation in reducing is obtained.

Bruch emphasizes that these 3 groups are not separate and distinct and that they are often combined.

Østergaard[19] described a group of 58 obese Danish children ranging in age from 4 to 14 years. Most of them had large appetites, and 80 per cent might be described as continuous eaters. Some were selective gourmets, others were indiscriminate eaters and gulped their food with little regard for its quality. They were, in the main, relatively inactive.

The social adaptation of the children was, for the most part, poor. Only about one-fourth could be said to relate normally to their peers. In some parental oversolicitude prevented normal social intercourse, others deliberately chose to isolate themselves. Some chose playmates who were considerably younger or older than themselves. In a few instances the children were in constant conflict with their surroundings in an effort to assert themselves.

In about one-fourth of the children, an unusually strong attachment to the mother, such as was described by Bruch, existed. In other instances there were overt parental rejection, parental indifference, parents who were overly strict and complaining, parents who expected too much scholastically. Other factors were death of a parent, separation of the parents, or an operation like tonsil-adenoidectomy or appendectomy. In about 15 per cent of cases no cause could be found.

Iversen[5] reported on 40 children with obesity ranging in age from 4 to 14 years. In only 16 of the 40 children were psychologic factors in the background prominent. Nonrejecting overprotection was most frequent. Other disturbing situations in the household were similar to those described by Østergaard.

Juel-Nielsen[10] was unable to recognize with any frequency in his Danish patients the characteristic exterior, social, and psychologic structure which Bruch found in her patients. In only 9 out of 61 children was he convinced of a causal relation between obesity and psychologic factors, and in only 3 was the setup like that described by Bruch.

In 12 patients the relationship of the obesity to psychologic factors was doubtful. In the remaining 40 children the obesity did not seem to be conditioned by specific psychogenic mechanisms or circumstances. In most of these the obesity could be easily explained by genetic factors and the eating habits of the family.

Endocrine disease only rarely causes obesity. Examples are such unusual conditions in children as Cushing's disease and hyperinsulinemia of various sorts. Hypothyroidism and hypopituitarism are not causes of obesity in children.

Addiction.—In many obese people the craving for food seems to have the same quality as the passion of the drug or alcohol addict for his particular habit. During periods of stress, they seek relief by nibbling food in the same way as does the smoker by puffing on a cigarette. Hamburger[6] classified 8 out of a group of 18 obese adults as food addicts. The hyperphagia is uncontrollable and constitutes a compulsive symptom. It often exists from early childhood. Hamburger was not able to relate it to external life events or to transient emotions.

It is interesting in this connection that, as a rule, smokers who stop their habit gain weight, probably because they nibble food instead of smoking.

SYMPTOMS

The diagnosis of obesity, as distinguished from simple overweight, can only be made clinically. However, available techniques for measuring total body fat are too elaborate for clinical use. Age-weight tables,

even age-height-weight tables, give only a measure of how much the individual deviates from the average. There is no way of knowing how much above the mean is abnormal, or even undesirable. Moreover, standards vary according to sex, race, socioeconomic status, and the time when the standards were set up, since children have been getting larger for a number of years. The general appearance of the patient, combined with an estimate of the amount of subcutaneous fat obtained by pinching the skin, are as good criteria as any. Estimates of the basal metabolic rate are of no value.

Most fat children are big eaters, but this does not seem to be always the case. Some eat continuously, others eat big meals only.

The importance of underactivity in the genesis of obesity has been minimized because of the mistaken ideas that exercise consumes little energy and that appetite increases when activity is stepped up. Most modern students of obesity regard underactivity as of major importance in obese children.

A study of the relation of inactivity to obesity in adolescent girls was reported by Johnson, Burke, and Mayer.[9] The obese girls were found to be relatively less active than the nonobese controls; indeed, inactivity was a more important factor in the obesity than overeating. The authors state: "In fact, the calorie intake of the obese group was significantly lower than that of the non-obese group with the relatively greater energy balance being consistently supplied by inactivity."

Presumably, energy intake is regulated on the basis of a small but definite amount of activity. If activity rises above the basal value, appetite and food intake increase. If, however, activity drops below the basal value, appetite and food intake do not decrease and an accumulation of fat takes place.

The burden of weight which obese children carry may discourage activity. In addition their psychologic problems—close attachment to the mother, the ridicule and teasing of peers—make for withdrawal from everyday childhood activities.

Aside from psychologic considerations, if any, which lead to obesity in a particular child, the obesity itself has an effect on the behavior and emotional life of the youngster and on his personal relations. Though moderate degrees of overweight are not looked down on in children as unesthetic and as a health hazard to the extent that they are in adults, nevertheless, obese children generally are the recipients of the cruel jibes of their peers.

Major concerns among obese children are their large size and feelings that they are ugly and socially inadequate. As a group they tolerate frustration poorly and tend to withdraw within themselves and daydream.

Fat children are, typically, advanced in height as well as weight, in ossification of the bony centers, and in the onset of puberty. The blood pressure is normal if account is taken of falsely elevated readings in fat persons.

Bruch found advanced mental development on the Stanford Binet tests in 119 obese children. The mean value was 110.7 ± 16.4, about 11 I.Q.

points above the average. There was some selection in the choice of cases since feeble-minded children were excluded.

The obese children did much poorer work on performance tests (Merrill-Palmer and Arthur point scale). Even greater disharmony was encountered in the "draw-a-person" test of Goodenough. A discrepancy in the performance on these different tests is generally taken to indicate severe emotional disturbance.

Confusion about their sex role is common in obese boys. Many are concerned about being rated as feminine, a reflection of the general attitude that fatness in a male indicates lack of masculinity. On the whole, interest in girls and failure to establish heterosexual relationships are frequent, although some have an active interest in the opposite sex and an adequate sex life. Homosexuality in adult life is infrequent. Obese girls show a similar confusion about their sex role. In them, also, homosexuality in later life is rare.

PROGNOSIS

The outlook in overweight children depends on the degree of the overweight, the age of onset, and the etiologic mechanisms. The method of treatment, important though it may be for the comfort of the patient and his family, has not been shown to influence the course of the obesity.

Moderate degrees of overweight are not infrequent in children and usually correct themselves. In the case of true obesity which is present before the age of 10 years, the prospect of later becoming slender is poor. The outlook is more favorable in boys than in girls. Loss of weight during adolescence is often temporary, being followed by a renewed increase later on.

A number of investigators have observed the appearance of schizophrenic symptoms in patients treated with reducing diets. Conversely, an increase in weight has been recognized as a sign of improvement, and weight increase is said to correlate well with a good prognosis.

Interesting in this connection are the observations of Kallmann[11] on twins with schizophrenia. He found that in 86 per cent of cases in one-egg twins both co-twins may be expected to have the disease, whereas in two-egg twins the expectancy was only 15 per cent. In 14 per cent of one-egg twins only one twin had schizophrenia. The only consistent difference found in these one-egg twins was that the immune one was stronger and weighed more than his sick co-twin.

Bruch followed a group of fat children into adult life. The study was incomplete since less than 50 out of the original 200 were reached. The results are therefore of doubtful accuracy and are presented by Bruch only as a rough index of what may be expected. In 15 per cent of the cases the follow-ups were slender and well adjusted emotionally. Twenty per cent were still obese but they were psychologically normal. A further 25 per cent were slender but badly adjusted, and 40 per cent continued to be obese and have emotional difficulties.

MANAGEMENT

Before recommending treatment, the physician must decide whether or

not the overweight is pathologic. If the youngster is only moderately overweight and neither he nor the parents seem concerned, it is wise not to interfere. It is a mistake to assume that overweight is invariably harmful. For some persons, overeating and being big is a balancing factor in their way of life. It represents the best form of adjustment that they have been able to make. They are unhappy and socially useless at lower weight levels. Dieting may lead to a weight reduction, but being thin is not a source of satisfaction to them.

In the treatment of obesity it is important to keep in mind that the etiologic factors are usually multiple; that dieting and medication alone are generally without lasting beneficial effect unless there is, at the same time, some understanding of the underlying causes; and that careful history taking is essential for proper management. Also, consideration should be given to questions of: To what extent do heredity, emotional factors stemming from disturbances in the home, and upsetting events influence the overweight? What is the child's reaction to his overweight? Does he himself want to get thin or does his mother want him to reduce? If he wants to get thin, why?

To be avoided by the physician is a censorious attitude. The obese child is not to be regarded as ridiculous, unsightly, or self-indulgent; and neither he nor his parents are to be blamed for his "grotesque" appearance.

A number of practical suggestions are offered by Mayer.[14] Obesity is to be viewed as a complex medical problem and not as a moral issue. Censorious sermonizing and shifting the entire responsibility onto the patient implying, thereby, that he is at fault are neither proper nor effective attitudes.

Scare propaganda is to be avoided. The association of obesity with increased mortality has been well established in adults but a similar relationship has not been demonstrated in children. It is preferable to emphasize weight reduction as a means of promoting a feeling of well-being and on esthetic grounds.

Mayer emphasizes the value of informing patients about the calorie value of foods as a guide during treatment. For example, many parents do not appreciate that an egg fried in butter has many more calories than a poached or boiled egg. The calorie value of an apple or an orange is approximately the same as that of a slice of bread. Potato chips, a common favorite of the muncher, have considerable calories. He also advises eating slowly since the satiety mechanism needs time for its operation.

Exercise should be encouraged. It is a sound way of using up ingested calories and it helps to promote nitrogen balance and muscle tone. Exercise does not increase appetite.

Amphetamine has limited usefulness in the treatment of obesity. It does decrease appetite at first, but this effect is temporary. Undesirable side effects are a dry mouth, bad taste in the mouth, and fetor oris. In the study by Adlersberg and Mayer[1] obese patients without amphetamine did as well as those with, after the initial period.

Phenmetrazine, a sympathomimetic drug, has been used with some success. The use of methylcellulose wafers which swell when swallowed may be

of value. There is no indication for using thyroid.

The diet for obese children in addition to being low in calories should contain an adequate amount of protein. Milk should be skimmed and the intake limited. For nibbling, while watching television, raw vegetables (carrots, cauliflower, and the like) may be substituted for higher caloric foods.

In prescribing diets for children specific directions are necessary. General instructions like cutting down on starchy foods, such as bread and potatoes, is of little value. A reasonable diet to start with in an adolescent is one of 1,200 calories.

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Dr. Peter William Vanace, c/o Camden Municipal Hospital, Copewood and Sheridan Aves., Camden, N. J.
Dr. Stanley M. Vickers, 1269 E. 18th St., Brooklyn 30, N. Y.
Dr. Herbert Lawrence Winograd, 14360 Cedar Road, University Heights 21, Ohio.
Dr. Frank Mitchell Wiygul, Jr., 1021 Mart 51, Jackson, Miss.
Dr. Herman Wolfson, 41 Market Square, Newington 11, Conn.
Dr. Rodger J. Zwemer, 1810 Wealthy St., SE, Grand Rapids, Mich.

SPECIAL FOREIGN CERTIFICATES:

Dr. Josephine Shou-Chen Chu, 3602 W. Dallas St., Houston 19, Texas.
Dr. Remedios M. Sunico, Grace-New Haven Hospital, NHRF, New Haven, Conn.
Dr. Constantin Missirliu, 18 Rue Guersant, Paris 17, France.
Dr. Carlos Marc Cossich M., 17 C No. 2-38 Zona 1, Guatemala City, Guatemala.
Dr. Natividad Z. Pangan, 2529 Fidil-Tondo, Manila, Philippines.
Dr. Edward James Turner, Department of Hematology, Montreal Children's Hospital, Montreal 25, Quebec, Canada.

Dr. Robert L. Jackson, chairman, Department of Pediatrics, **University of Missouri School of Medicine, Columbia,** has been appointed chairman of the Committee on Infant Nutrition by the Food and Nutrition Board of the National Research Council, Washington, D. C. Other members of the committee are Dr. Harry H. Gordon, Baltimore; Dr. Paul György, Philadelphia; Wendell H. Griffith, Ph.D., Los Angeles; Dr. Charles U. Lowe, Buffalo, N. Y.; and Dr. Joseph A. Johnston, Detroit.

Two fellowships have been made available by the United States Public Health Service for training in pediatric psychiatry at the **State University of New York.** The program will be under the direction of Dr. Alfred M. Freedman.

The fellowships are one year in duration and salary depends upon extent of training. These fellowships have been established to give a physician who has training in pediatrics one year's experience in psychiatric aspects of pediatric practice. Fellows may begin their training on July 1, 1959, or thereafter. They must be citizens of the United States or have declared their intention to become citizens.

Through clinical work and participation in seminars, the fellow will gain knowledge of the inter-relationship of emotional and social factors and physical illness. The fellow will also have the opportunity to participate in the research program of the Pediatric Psychiatry Unit, which currently is concerned with long-range developmental studies of prematurely born children, varying aspects of brain damage, and biological aspects of mental illness. The fellow will also have an opportunity to be involved in other activities of the Department of Pediatrics.

Communications in regard to these fellowships should be addressed to: Richard L. Day, M.D., Professor of Pediatrics, State University of New York, Downstate Medical Center, 450 Clarkson Ave., Brooklyn 3, N. Y.

The twenty-seventh annual series of the Benjamin Knox Rachford Lectureships will take place in Cincinnati, Ohio, on Tuesday and Wednesday evenings, April 21 and 22, 1959, at 8:30 P.M. Dr. Lorimer Dods, Professor of Child Health at the University of Sydney, Australia, will deliver these lectures in the auditorium of the Children's Hospital Clinic and Research Building. On April 21 Dr. Dods will lecture on "Paediatrics in the Antipodes," and on April 22 his subject will be "Some Paediatric Philosophy."

The Honolulu Pediatric Society is sponsoring the Golden Jubilee Celebration of Kauikeolani Children's Hospital from April 19 to 22, 1959, in Honolulu, T.H. Guest participants for the scientific program will be Dr. J. Roswall Gallagher, Chief Adolescent Unit, Children's Medical Center, Boston, Mass., and Dr. C. Tague Chisholm, Assistant Clinical Professor of Surgery, University of Minnesota. The topics will be centered on problems of adolescence and of pediatric surgery. The Princess Kaiulani Hotel Meeting House will be the center for the scientific sessions.

Reservations may be made with the Golden Jubilee Committee, Children's Hospital. Honolulu, T.H., or directly through the A. M. P., Academy of Pediatrics, c/o E. H. Christopherson, 1801 Hinman Ave., Evanston, Illinois.

Books

Tumors and Tumorous Conditions of the Bones and Joints. Henry L. Jaffe, M.D., Philadelphia, 1958, Lea & Febiger, 629 pages. Price $18.50.

This new book on bone and joint tumors by Dr. Henry L. Jaffe fills an important gap in the medical literature for the surgeon, orthopedic surgeon, radiologist, and pathologist with a comprehensive and exhaustive survey of these conditions with careful, knowledgeable, clinical, roentgenologic, and pathologic correlations. This correlative treatment emphasizes Dr. Jaffe's beliefs that the proper diagnosis of bone tumors can be made only by close interplay between the surgeon, roentgenologist, and pathologist. He considers each lesion by itself, without attempts at a comprehensive classification. For each of these he gives a justification out of his very extensive experience for its separation from other lesions, the incidence, and clinical,

roentgen, and pathologic findings, differential diagnosis, treatment, and prognosis. These are accompanied by carefully chosen, beautifully reproduced, highly informative roentgenograms of both clinical cases and gross pathologic specimens, often of the same case, as well as superb microphotographs. These photographs accompanied by legends recording the pertinent clinical data form a veritable atlas of bone tumor pathology. The bibliography is carefully chosen, ample, and current. Of all the sections, perhaps the microscopic description is the weakest, for Dr. Jaffe does not emphasize sufficiently the variations and atypical features of the microscopic picture, particularly of the more common lesions which so plague the practicing pathologist. There may be some quarrel with the distribution of space alloted to lesions of great rarity, yet a strong point may be made for this, since these states are among the most likely to be misdiagnosed, simply by not being considered.

Although some reference is made to sex and age incidence, and distribution within the body, the over-all frequency of each lesion type is given in a heterogeneous fashion, such as "very rare," "most frequent," "5 cases in the author's experience," which makes it hard to assess overall importance of each lesion for the student.

To one reading the book chapter by chapter, the one marring feature lies in the repeated use of noun and adjective forms as verbs, two of the most glaring being "spongified" and "porotified," and the redundancy of certain frequently recurring, ill-chosen phrases such as "lesional area." The book is carefully edited and beautifully printed. It will find a welcome and well-deserved place on the reference shelf of those dealing with such lesions.

J. M. C.

Chronik der Kinderheilkunde. Albrecht Peiper, Leipzig, 1958, Georg Thieme, 527 pages. Price 51.20 DM.

A third edition of the excellent history of pediatrics by Prof. Peiper, Director of the Children's Clinic in Leipzig. The first portion of the book presents the history of pediatrics in the usual way, from the ancient cultures down through the ages to the present times. This is followed by chapters on social pediatrics, including such subjects as orphanages, hospitals for children, and the handicapped child. The next subject is the development of what we term "scientific" pediatrics, to which the German pediatricians contributed so much fifty to seventy years ago when German medical science was dominant. The final portion of the text presents the history of a number of pediatric diseases. The book is scholarly, and the fact that the first edition was published only seven years ago speaks for its reception in the German-speaking countries. The third edition contains references as late as 1958. The chief criticism is that it is overweighted with German source material. The book contains a mass of interesting material and should be on the shelves of our pediatric clinics and medical libraries, despite the fact that the number of pediatricians who read German is rapidly diminishing outside the German-speaking countries. The international situation has quite changed in the last forty years, and recently some German periodicals are publishing editions in English so that their scientific medical work, which has undergone a revival in the last few years after a period of decline, will be available to those not familiar with the language.

Häufigkeit und Art meteorotroper Erscheinungen im Kindesalter. Wolfgang Menger, Basel, 1958, S. Karger, 131 pages. Price 20.80 S. Fr.

The effect of meteorological conditions on the health of man and their role in the production of certain diseases is a very old story, whose importance, except to a few, largely disappeared with the advances of medical science. That many diseases are seasonal is well recognized, and that temperature-humidity relationships affect one's well-being is accepted. The author attempts to link many childhood diseases with meteorological conditions but leaves the reviewer unconvinced of a direct relationship in most instances. Nevertheless, it is an interesting discussion to anyone with an open mind.

Developmental Potential of the Preschool Child. Else Haeussermann, New York, 1958, Grune & Stratton, Inc., 285 pages. Price $8.75.

The author is Educational Consultant to the Division of Pediatric Psychiatry at the Jewish Hospital in Brooklyn. It is a rather technical discussion of the methods developed and used by the author in evaluating the potential development of retarded children and children with handicaps needing rehabilitation. One gathers there is no short cut to this important problem. The book will be of chief interest and use to the workers in the many clinics that are being established in this field rather than to the pediatrician in practice.

Clinical Enzymology. Edited by Gustav J. Martin, Sc.D., Boston, 1958, Little, Brown & Co., 241 pages. Price $6.

A discussion of the enzymes used in clinical medicine. Dr. Martin, the Editor, contributes four of the seven chapters. The subjects include protein biology, the chemistry and biochemistry of enzymes used clinically, their diagnostic use, and their parenteral use in clinical medicine. The various chapters collect the many studies and reports on enzymes and are followed with extensive bibliographies. While the reader is left with the feeling that there is still much to be learned about enzymes and their use in clinical medicine, this volume summarizes our present knowledge.

Immunization Information for International Travel. Public Health Service, Washington, D. C. Obtainable from Superintendent of Documents, Government Printing Office, Washington 25, D. C. Price 30 cents.

Revised booklet as of June, 1958. With the tremendous growth in foreign travel in recent years, physicians are not only called upon to give required immunization but are also questioned as to what immunizations are required or desirable for certain countries. This excellently prepared and printed booklet contains the answers. It will be most useful to the practitioner.

Dentistry for Children, ed. 4. J. C. Brauer, W. W., Demeritt, L. B. Higley, R. L. Lindahl, M. Massler, and I. Schour, New York, 1958, McGraw-Hill Book Co., Inc., 492 pages. Price $11.00.

A revised fourth edition of the text for students at the undergraduate and graduate levels, chiefly by the pedodontic group at the University of North Carolina School of Dentistry.

Year Book of Pediatrics, 1958-1959 Series. Chicago, 1958, Year Book Publishers, Inc., 496 pages. Price $7.50.

Dr. Sydney S. Gellis continues to make the Year Book of interest and value. The large number of pages given to abstracts on the newborn and premature infant reflect the current interest in this field. The comments by "authorities" add very much to the value of the book.

Untersuchungen zur klinischen Problematik der progressiven Muskeldystrophie, Joachim Brugsch and K. Brockmann-Rohne, Leipzig, 1958, Georg Thieme, 54 pages. Price 9.80 DM.

A monograph based on the study of 214 patients with progressive muscular dystrophy. Considerable emphasis is placed on classification. As a whole, nothing particularly new is found in the monograph.

The Ureterovesical Junction. John A. Hutch, M.D., Berkeley and Los Angeles, 1958, University of California Press, 178 pages. Price $7.50.

A monograph by Dr. Hutch of the University of California Medical School in San Francisco. Of chief interest to the urologist. Beautifully printed and illustrated.

Editor's Column

ADVANCES IN THE CONTROL OF CANCER IN INFANTS AND CHILDREN

ALTHOUGH advances in many fields of medicine have contributed to an improved prognosis in certain types of malignant neoplasms encountered in early life, well over 3,500 infants and children die each year in the United States as a result of some form of cancer.[1] Moreover, there is some evidence to indicate an actual as well as a relative increase in the incidence of cancer in early life.[2] Since malignant neoplasms, including leukemia, are now the single leading cause of death from disease in children from 3 to 14 years of age, it behooves us to re-evaluate our concepts of neoplasia in infants and children in an attempt to control the loss of life currently occurring as a result of this group of diseases.

Obviously complete control of cancer must be based upon an understanding of the fundamental nature of neoplasia. To date, in spite of the expenditure of tremendous amounts of time, money, and effort on basic research, knowledge of the essential defect responsible for the uncontrolled growth of neoplastic cells is still incomplete. Important observations have been made, and it is even possible that the facts requisite for a solution of this problem are already available. If so, they have not been integrated with each other in such a manner as to afford a true concept of the nature of cancer. The continued investigations of widely divergent disciplines of science, directed toward the ultimate solution of this problem, must not be curtailed, but the importance of perceptive integration of the facts which are currently available and which will be forthcoming must not be minimized.

In the absence of an understanding of the basic nature of neoplasia, what practical advances have occurred in recent years? Within little more than a decade the treatment of acute leukemia has progressed to such an extent that many children with this disease may now lead a comfortable life for months and, in some instances, even years. Although leukemia continues to be invariably fatal, the importance of the advances made in its treatment can hardly be overestimated. Not only are these of obvious benefit to the patients and their families, but they have been of incalculable value in stimulating further investigation into the nature of neoplastic cells. It is now apparent that certain neoplastic cells can be rather selectively destroyed by depriving them of essential elements. As in the case of bacterial resistance to antibiotic agents, however, it remains to be learned by what means resistance on the part of the neoplastic cells to the action of antineoplastic agents can be prevented.

But the practical advances have by no means been confined to the use of systemic antineoplastic agents, and indeed a reduction in the mortality rate of certain neoplasms of early life was observed prior to the advent of many of these agents. It is impossible to evaluate the relative importance of advances in anesthesiology, surgery, replacement of body fluids, chemotherapy, and radiotherapy in the increased survival rates of infants and children with certain forms of cancer. Certainly, however, improved methods of treatment of cancer will not yield optimal results unless coupled with earlier diagnoses. Recognition of the existence of cancer as a real problem in early life and of the fact that a significant number of infants and children with malignant neoplasms can be cured should stimulate efforts toward earlier diagnosis and treatment and should thus enhance the survival rates of these patients.

Cancer, including leukemia, is responsible for 18 per cent of the deaths from disease in children from 1 to 14 years of age; however, it is an infrequent cause of morbidity. For example, at St. Christopher's Hospital for Children during the five years preceding June 30, 1958, only 0.81 per cent of all hospital admissions were because of cancer; during this same period, 12 per cent of the autopsies performed were on patients who had died of some type of malignant neoplasm. More instances of cancer are observed during the first five years of life than during either of the two ensuing five-year periods[1, 3, 4]; over one-half of the leukemias observed in children occur in the age period of from 0 to 4 years.[5] Although certain types of neoplasms are now associated with a hopeless or extremely grave prognosis, e.g., leukemia, medulloblastoma, and Ewing's tumor, reports obtained from centers where there is particular interest in the problem of neoplasms would indicate that such a pessimistic attitude with respect to neoplasms in general in early life is not justified. Thus, apparent cures have been reported in some series in from one-third to more than one-half of the patients with Wilms's tumors. The best survival rates have been obtained in infants less than 12 months of age.[6] The survival of patients with neuroblastoma is only slightly less, and again the results appear to be better in young infants than in older children. It has been estimated that almost one-half (46 per cent) of the children with intracranial tumors are at least theoretically curable, and that approximately 90 per cent of those with cerebellar astrocytomas may be cured.[7] Even patients with osteosarcomas, considered by many to have a hopeless prognosis, may not be as uniformly fatal as formerly believed; in a large group of patients of all ages recently reported by Dahlin,[8] the ten year survival rate was 15 per cent.

Although the above figures are obviously selected and in some instances are based upon relatively small numbers of patients, they give some indication of the results which can be obtained with a variety of the malignant neoplasms encountered in early life. The possibility of cure, even with existing methods of therapy, is far better for many of these neoplasms than for such common tumors of adult life as carcinoma of the lung or of the stomach. Certainly there is every reason to increase our effort to learn more concerning the basic nature of neoplasms and, in the meantime, to use

more effectively the methods now available for the control of cancer in early life.

JAMES B. AREY

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